A COMPARATIVE STUDY OF EFFICACY OF CONTINUOUS VERSUS INTERMITTENT IRON THERAPY FOR THE TREATMENT OF IRON DEFICIENCY ANEMIA IN CHILDREN OF AGE GROUP 6 MONTHS TO 5 YEARS.

Dissertation submitted to

THE TAMILNADU DR.M.G.R.MEDICAL UNIVERSITY

In partial fulfilment of the regulations for the award of degree of

M.D DEGREE (PEDIATRICS) BRANCH VII

INSTITUTE OF SOCIAL PEDIATRICS

STANLEY MEDICAL COLLEGE

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APRIL 2016

DECLARATION

I, **Dr. C. KRISHNAKUMAR** solemnly declare that the dissertation titled **"A COMPARATIVE STUDY OF EFFICACY OF CONTINUOUS VERSUS INTERMITTENT IRON THERAPY FOR THE TREATMENT OF IRON DEFICIENCY ANEMIA IN CHILDREN OF AGE GROUP 6 MONTHS TO 5 YEARS"** was done by me at **Government Stanley Medical College during 2014 - 2016** under the guidance and supervision of my chief **Prof. S. LAKSHMI M.D, D.C.H.**

The dissertation is submitted to **The Tamilnadu Dr.M.G.R Medical University** towards the partial fulfilment of the rules and regulations for the **M.D. Degree Examination - BRANCH VII - in Pediatrics**.

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ACKNOWLEDGEMENT

It is with immense pleasure and gratitude that I thank **Dr.ISAAC CHRISTIAN MOSES M.D., DEAN, STANLEY MEDICAL COLLEGE** for bestowing me the permission and privilege of presenting this study and for enabling me to avail the institutional facilities.

I am gratefully indebted to **Prof. S. SHANTHI M.D, DCH**, Director, Institute of Social Pediatrics, Stanley Medical College for her valuable guidance and motivation .

I am very grateful to both my chiefs, **Prof. Lakshmi M.D, DCH., Prof. Devi Meenakshi M.D, DCH and Dr. M. A. Aravind MD., DCH.,** for guiding through my dissertation process and providing departmental resources for the conductance of this study.

I am extremely thankful to **Dr.Elango M.D, DCH** Pediatric Registrar, for his valuable suggestions and guidance during this study.

I express my gratitude to the Assistant Professor of PICU **Dr. Ekambaranath M.D** for his valuable help and guidance for this study.

I sincerely thank my Assistant Professor **Dr.P. Venkatesh M.D** for his timely help and support throughout the course of this study.

I thank my Assistant Professors **Dr.Radhika M.D, Dr.Raja M.D, Dr.Vinoth M.D, Dr.Kumar DCH, Dr.Sankara Narayanan M.D, Dr. Senthil kumar MD and Dr. Parveen MD.,** for their valuable support.

I sincerely thank all the patients and their parents who participated in this study.

I thank all the PICU staff nurses for their immense help in conducting this study.

Finally I thank all the post graduates in the Department of Pediatrics in our Stanley Medical College who have helped me through thick and thin. It was an immense pleasure working with all.

CONTENTS

ABBREVIATIONS

ID – Iron deficiency

IDA – Iron deficiency Anemia

WHO – World Health Organisation

CBC – Complete Blood Count

Hb – Hemoglobin

PCV – Packed Cell Volume

TC – Total Count

DC – Differential Count

O_2 – Oxygen

IRP – Iron Regulatory Protein

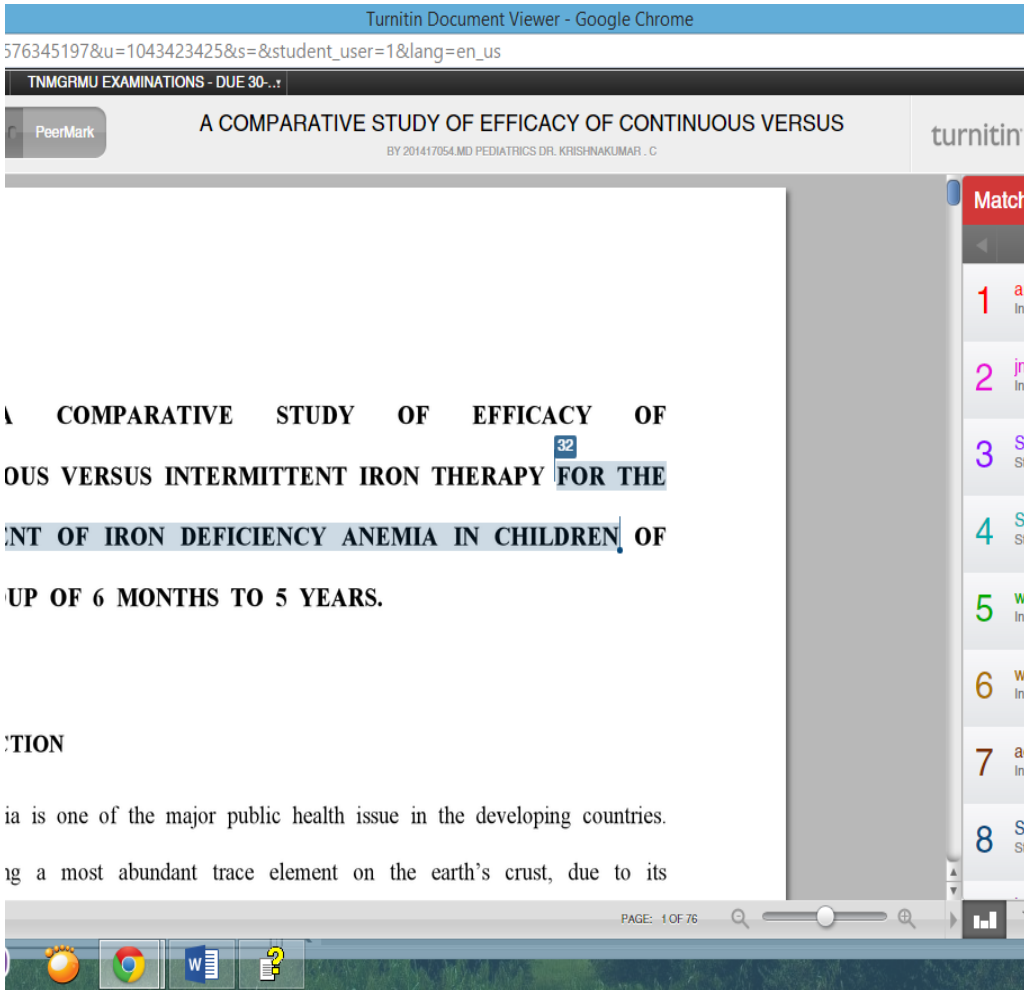
kDa – kilo Dalton

DMT1 – Divalent metal (ion) transporter 1

MRI – Magnetic Resonance Imaging

Fe^{2+} – Ferrous Iron

Fe^{3+} – Ferric Iron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Dr. C. Krishnakumar MD (Peds) Post Graduate Student

Aim and Objective:

To study the outcome of Iron Deficiency Anemia by measuring the changes in Hemoglobin concentration in Continuous versus Intermittent iron therapy in children of age 6 months to 5 years over a period of 12 weeks intervention and to study the improvement in other hematological parameters like Hematocrit, MCV and compliance and adverse effect profile in both groups.

Methods and materials:

140 children with iron deficiency anemia fitting into the inclusion criteria were enrolled. Randomized into intermittent n = 70 (biweekly) and daily iron supplementation group (n = 70) and started on 3mg/kg of elemental iron in both groups. Followed at 3-5 days for evaluating reticulocytosis, at 4 weeks at assess rise in hemoglobin and after 12 weeks for reassessing all the hematological parameters done initially and adverse effect profiles.

Observation and results:

Out of the 140 children, 68 in intermittent group and 65 in daily supplementation group were able to complete the study. Both the intermittent and daily iron supplementation group showed similar response to iron therapy in terms of increase in Hemoglobin, Hematocrit and MCV. But the daily supplementation group showed significant increase in serum ferritin levels ($p < 0.001$) as compared to intermittent iron supplementation group.

However the compliance and adverse effects were lower in intermittent iron therapy group statistically significant than daily iron supplemtation group.

Conclusion:

From the study, it was concluded that intermittent iron therapy is as effective as daily iron therapy in improving anemia in children of age 6 months to 5 years with improved drug compliance and lesser adverse effects.

A COMPARATIVE STUDY OF EFFICACY OF CONTINUOUS VERSUS INTERMITTENT IRON THERAPY FOR THE TREATMENT OF IRON DEFICIENCY ANEMIA IN CHILDREN OF AGE GROUP 6 MONTHS TO 5 YEARS.

INTRODUCTION

Anemia is one of the major public health issues in the developing countries. Despite being the most abundant trace element on the earth's crust, its relative insoluble nature and poor bioavailability makes iron deficiency anemia as one of the most prevalent nutritional deficiency disorder.

In spite of sustained efforts to reduce the burden of nutritional disorders, iron deficiency anemia is still highly prevalent in many parts of the world[1]. Around the world, over two billion people i.e., about 30% of the total population of the world still remain anemic. The major cause being iron deficiency. In under developed regions, this scenario is further complicated by infectious diseases.

Worldwide, 47.4% of children between 0 to 5 years of age are anemic, with the burden being greatest in low and middle income countries. More than 50% of the total cases of anemia were attributed to iron deficiency.[2] The prevalence of Iron deficiency varies between locations but is estimated by the World Health Organization to be 2.5 times higher than that of Iron deficiency anemia in most places.[3]

Iron deficiency is one major public health condition that is emerging onto an epidemic proportion. It causes more morbidity than any other condition. Since most of the early manifestations of iron deficiency are subtle, iron deficiency imparts its heaviest overall toll in terms of morbidity, early deaths and economic losses.

Invisible, yet ubiquitous in many developing countries, the true toll of iron deficiency and anemia lies hidden in the statistics of overall death rates, maternal hemorrhages, reduced school performance and lowered productivity. The health consequences are stealthy but devastating, invisibly eroding the development potential of individuals, societies and national economies.

Children are at particular risk of Iron deficiency because of rapid growth with expanding erythroid mass and high tissue iron requirements [4]. In infants, antenatal and perinatal factors can influence iron status. Major risk factors for iron deficiency anemia in young children are low birth weight and preterm delivery where the body iron stores are limited.

The major cause for the very high prevalence of iron deficiency anemia are due to low dietary iron intake and the poor bioavailability of the ingested iron. Prolonged milk feeding and improper complementary feedings are also associated with Iron deficiency, Iron deficiency anemia, and other micronutrient deficiencies [5].

Causes and epidemiology of anemia in 2 to 5 year olds appear to differ from those in infants. Children 2 to 5 years of age are more likely to be ambulant and where sanitation is poor, can acquire hookworm infection, which can result in Iron deficiency. The burden of anemia from malaria may also decline after infancy.

Our national surveys (fig.1) show the prevalence of anemia at 12 to 23 and 48 to 59 months is, 83.0% and 53.0% respectively. This is similar to other developing countries with, 69.1% and 38.2% in Ethiopia, 72.7% and 42.0% in Malawi, 70.6% and 20.7% in Nepal, and 71.5% and 45.6% in Zimbabwe[6].

In Indian scenario, the percentage of male and female children (6-59 months) with any type of anemia was reported as 69% and 69.9% respectively, severe anemia was reported for 3.2 % male children and 2.7% female children. Anemia was more prevalent in rural areas (71.5%) than Urban areas (63%).

Maternal education status plays an important role in the nutritional status of the child. This can be inferred from the data showing significantly low prevalence of anemia in children of mothers with atleast 12 years of education (55.4 %), than with uneducated mothers, where the prevalence is as high as 74.5%. This highlights the importance of female education in alleviating the burden of anemia.

Economic status of the family also plays a major role in determining the nutritional status of the child. This fact is supported by numerous nutritional survey results.

National Family Health Survey 3 (2005-06), reveals 76.4% of children (6-59 months) in the lowest wealth index are suffering from anemia whereas 56.2% children of the highest wealth index are suffering from anemia. This is indicative of the reality that affluence alone cannot rule out anemia among children.

Children are particularly vulnerable for iron deficiency anemia. Iron deficiency in children may have functional consequences beyond anemia. These include impaired motor and cognitive development and physical growth[3]. Iron supplementation has been thought to improve these outcomes,[8] but some impairment may be irreversible[9]. Conversely, there are concerns that iron may produce adverse effects, including increased susceptibility to infection[10].

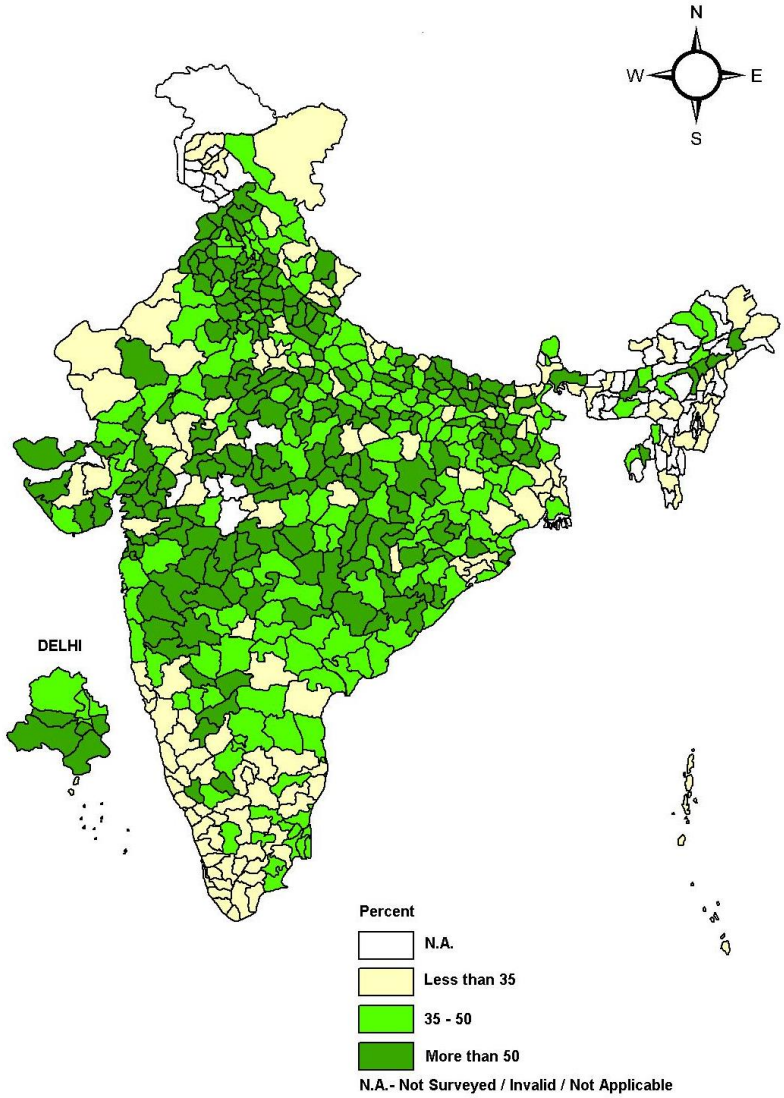

Figure 1: Geographical distribution of Iron deficiency Anemia. (Source NFHS 3)

Iron supplementation is considered a standard approach for treatment and prevention of Iron deficiency anemia[11]. Supplementation programs for other micronutrients, such as vitamin A are more successful partially because there are few side effects and unlike iron, daily supplementation is not necessary.

However, few studies have reported that in anemic rats, the supplementation of iron twice a week was found to produce comparable results as with daily iron supplementation. The theoretical explanation would be that daily supplementation of iron leads to a strongly reduced absorption several days after initiation, whereas with intermittent supplementation the level of absorption would remain much higher.

Ideally, supplementation should achieve maximal absorption with minimal side effects. As a public health measure WHO recommended that all preschool-aged children should receive a course of daily iron supplementation where the baseline prevalence of anemia is >40%[7].

Intermittent treatment with oral iron preparations in preschool and school aged children has recently been evaluated by a systematic review, which found that intermittent iron was effective in reducing anemia, although less so than daily iron[12]. On the basis of this analysis, WHO revised the guidelines recommending intermittent iron for prevention of anemia in children[14]. However these studies did not include a comparison of daily iron with control.

From the public health point of view, intermittent dose of iron preparation seems to be more convenient when compared to daily dosing. Moreover, it is economic, safer in terms of avoiding constant excess iron in the gastrointestinal tract and offer greater coverage for the children in the community.

AIM AND OBJECTIVES

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AIM:

To study the outcome of Iron Deficiency Anemia by measuring the changes in Hemoglobin concentration in Continuous versus Intermittent iron therapy in children of age 6 months to 5 years over a period of 12 weeks intervention.

Secondary objectives:

To study the changes in other hematological parameters pertaining to Iron deficiency anemia like Serum Ferritin and Red cell indices like Hematocrit, MCV and compliance and adverse effect profile in the Intermittent and daily iron therapy group.

PHARMACOLOGICAL PROPERTIES OF IRON

As the normal life span of erythrocytes is about 120 days, there needs to be method for their continuous replacement. This process is called *erythropoiesis.* New cell production must be matched to basal needs and states of increased demand. Erythrocytosis can be augmented by more than 20 fold in response to anemia or hypoxemia. Similarly, leukocytosis can increase dramatically in response to a systemic infection. thrombocytosis can increase 10–20 times when platelet consumption results in thrombocytopenia.

The control of blood cell production is complex. Hematopoietic stem cells are bone marrow derived cells that possess self-renewal and lineage commitment, resulting in the newly produced cells that are destined to differentiate into the distinct blood-cell lineages. Major steps in this process occurs in the bone marrow cavities of flat bones like the vertebral bodies, skull and pelvis as well as in the proximal regions of long bones.

Hematopoiesis involves a complex interactions between hematopoietic stem and progenitor cells in the bone marrow and the surrounding complex macromolecules. The process is regulated by various hematopoietic cytokines.

Production of blood cells also requires an adequate provision of various trace elements like Iron , Copper and cobalt, and vitamins including folic acid, vitamin B12, Vit B6, Vit B2, and Vit C. Deficiencies of any of these micronutrients results in characteristic anemia or rarely a general failure of hematopoiesis.

Treatment of a specific deficiency state depends on the accurate diagnosis of the cause of anemia, knowledge about the correct dose of the preparation used, the use of these agents in various combinations and the expected outcome.

Iron deficiency is the most common nutritional cause of anemia in humans. Causes of iron deficiency includes inadequate dietary iron intake, malabsorption, acute or chronic blood loss and an increased requirement states like childhood and pregnancy. In severe deficiency states, it results in a characteristic microcytic, hypochromic anemia.

However, the impact of iron deficiency is not limited to the erythrocytes. Iron also is an essential component of many macromolecules and enzymes like myoglobin, heme containing enzymes such as the cytochromes, catalase - peroxidase and the metallo-flavoprotein enzyme like xanthine oxidase and the mitochondrial enzymes like glycerol phosphate oxidase.

Iron deficiency can affect muscle metabolism irrespective of the state of anemia and tissue oxygen delivery. This process reflects the

importance of iron on mitochondrial metabolism in the muscle. Iron deficiency is well established cause of behavioral and learning problems in children and abnormalities in catecholamine metabolism.

Recognition of the ubiquitous role of iron in the overall metabolism leads to the concept of early and accurate detection of iron deficiency and in its prevention.

Our understanding of iron metabolism are based on researches in 1937, with the work of McCance and Widdowson[15] on iron absorption and excretion and Heilmeyer and Plotner's estimation of iron levels in plasma. T*ransferrin* was discovered in 1947 by Laurell[15] who described it as a plasma iron transport protein.

In 1948, Hahn et al.,[16] first used radioactive isotopes to estimate iron absorption. He proposed the role of the intestinal mucosa to regulate the absorption of iron. Subsequent Huff et al., made isotopic studies of internal metabolism of iron. Later development of other practical clinical measurements like serum iron, transferrin saturation, plasma ferritin, and erythrocyte protoporphyrin permitted more accurate definition and detection of the body's iron store status and iron-deficient erythropoiesis.

Iron and the Environment

Iron is found in the environment largely as insoluble ferric oxide or hydroxide or as polymers. In this form, its biological availability is low, unless enhanced by acid or chelating agents. Bacteria and some plants produce high-affinity chelating agents that absorbs iron from the surrounding environment.

Most mammals do not have difficulty in acquiring iron. This is explained by a sufficient iron intake and perhaps also by a greater efficiency in absorbing iron. However in Human beings, there seems to appear an exception. Although total dietary consumption of elemental iron in humans usually exceeds requirements, the bioavailability of the iron in the diet is low.

Metabolism of Iron.

The body iron stores (fig.2) can be divided into essential iron-containing compounds and excess iron, which is held in storage. Quantitatively, hemoglobin accounts for the major share of essential fraction.

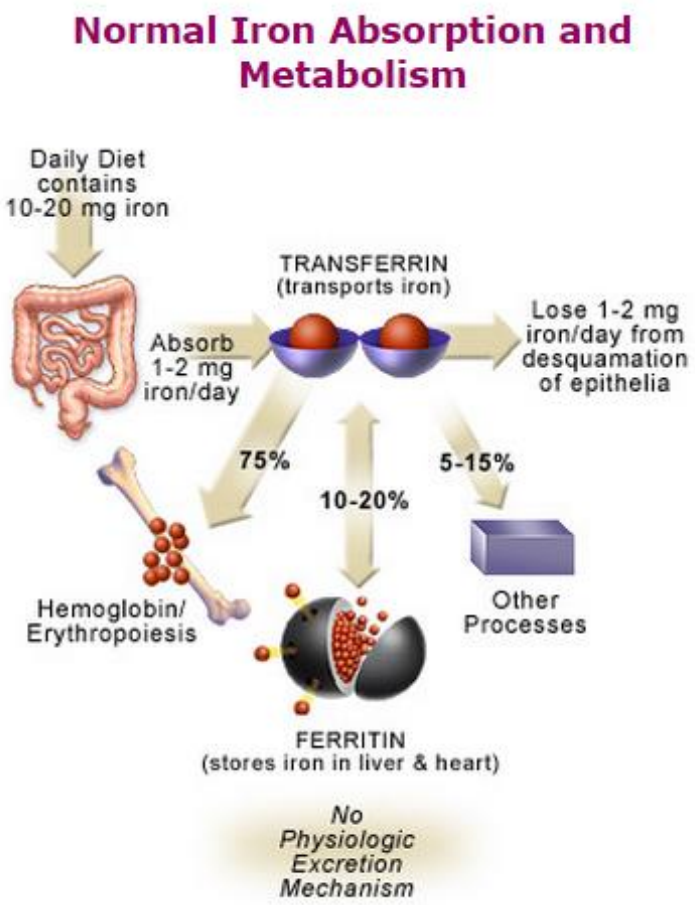


Figure 2: Normal Iron metabolism

Hemoglobin is a protein with a molecular weight of 64,500 Da. It contains four atoms of iron per molecule, amounting for 1.1 mg (20 umol) of iron per milliliter of erythrocytes. Various other forms of essential iron are myoglobin and a variety of heme and non-heme iron dependent enzymes.

Ferritin is a protein, functions as iron storage complex. It either exists as individual molecules or as aggregates. Apoferritin has a

molecular weight of about 450,000 Da. It is composed of 24 polypeptide subunits that form an outer shell. Within this resides a storage cavity for iron as polynuclear hydrous ferric oxide phosphate. Upto 30% of the weight of ferritin may be iron that accounts for about 4000 atoms of iron per ferritin molecule.

Aggregates of ferritin forms hemosiderin. It can be seen under light microscopy. It constitute about one-third of normal stores. Its fraction that increases as stores enlarge. Reticuloendothelial system and the hepatocytes constitutes the two major areas for storage of iron. But muscles also offer some storage.

Internal transport of iron is caused by the plasma protein called transferrin. Transferrin is a 76-kDa glycoprotein. It carries two binding sites for ferric iron. Iron is exchanged from transferrin to intracellular sites by a specific plasma membrane bound transferrin receptors. The iron-transferrin complex attaches to the cell surface receptor, and the transferrin-receptor complex is internalized by means of clathrin-coated pits by receptor-mediated endocytosis. A proton-pumping ATPase located within the endocytosed complex lowers the pH of the intracellular vesicular compartment (the endosomes) to about 5.5. Subsequently Iron dissociates and the receptor returns the apotransferrin back to the cell surface for release into the extracellular environment.

Cells regulate their expression of transferrin receptors and intracellular ferritin in accordance to the iron demand. The synthesis of transferrin receptors in the cytoplasmic membranes and apoferritin is regulated post-transcriptionally by two **Iron-Regulatory Proteins 1 and 2** (IRP1 and IRP2).

These Iron regulatory proteins are cytosolic RNA-binding proteins that combines with iron regulating elements (IREs) present in the 5' or 3' untranslated segments of mRNA encoding apoferritin or the transferrin receptors, respectively. Binding of these IRPs to the 5' IRE of apoferritin mRNA represses translation. Alternatively, its binding to the 3' IRE of mRNA causes transcription of the transferrin receptors and increases transcript stability, thereby increasing protein production.

When body iron store is abundant, IRP2 undergoes rapid proteolysis and IRP1 is converted from a RNA-binding protein into aconitase. This is an enzyme that catalyzes the interconversion of citrate and isocitrate in glucose metabolism. This results in increased production of apoferritin and thereby decreased production of transferrin receptors.

Conversely, when iron is in short supply, these Iron regulatory Proteins accumulate, thereby repressing translation of apoferritin while enhancing synthesis of transferrin receptors.

The total amount of transport iron in the plasma amounts to a total of 30-40 mg or 0.46 mg/kg of body weight[17]. The major internal

circulation of iron is between the erythroid mass and reticuloendothelial cells. Around 80% of the iron in plasma goes to the red marrow of the bones, to be incorporated into new erythrocytes. These normally circulate for 120 days before being destroyed by the reticuloendothelial cells of spleen. Here a portion of the salvaged iron and returned to the plasma bound to transferrin, whereas other portion is packaged into the ferritin stores of reticuloendothelial cells. This is returned to the circulation more gradually.

Isotopic studies of iron metabolism indicate some degree of iron loss in this process. Here the defective cells or unused portions of their iron are transferred to the reticuloendothelial cell during maturation, bypassing the circulating blood. As in cases of abnormalities in erythrocyte maturation, the predominant portion of iron assimilated by the erythroid marrow is rapidly localized in the reticuloendothelial cells as defective red-cell precursors are lysed. This process is termed as *ineffective erythropoiesis.*

The rate of iron turnover in the body may be reduced by more than half with conditions like red-cell aplasia, with all the iron directed to the hepatocytes for storage.

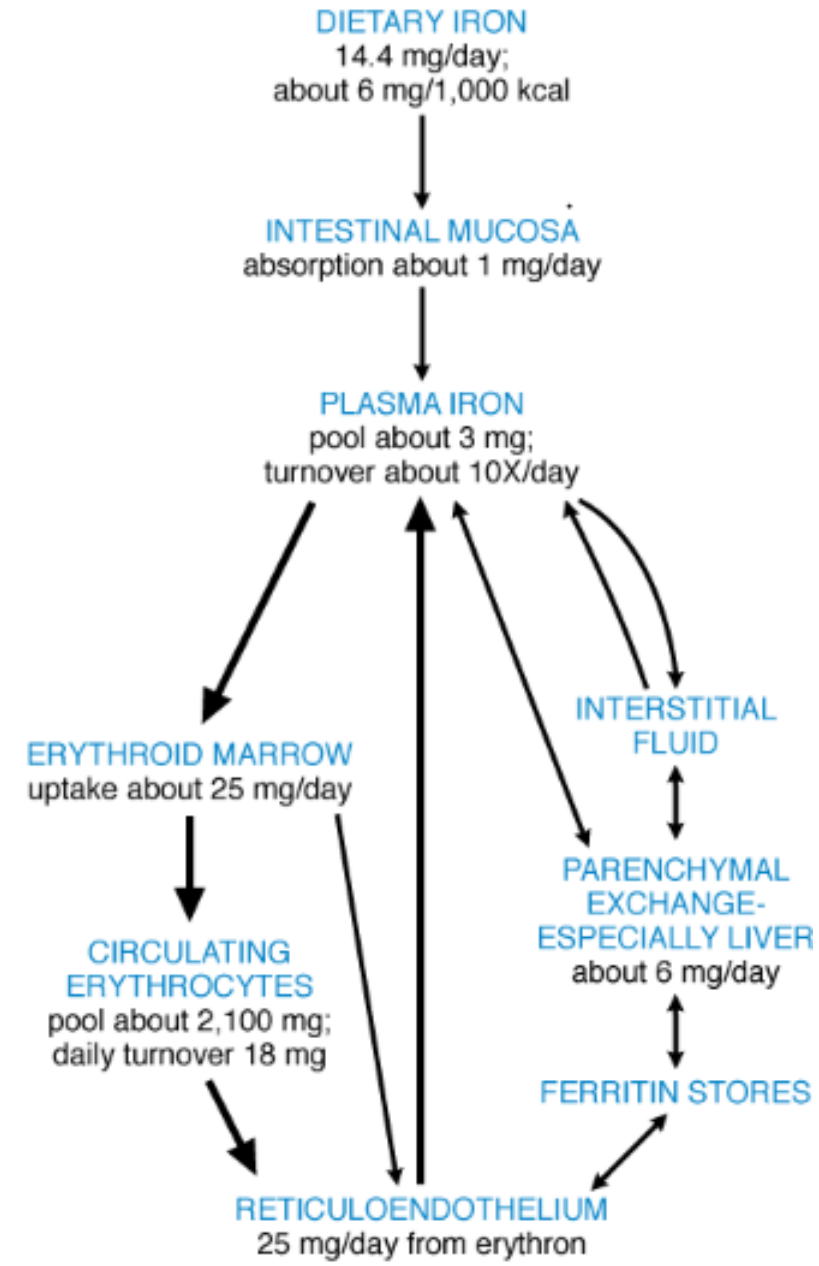


Figure 3: Distribution of body Iron stores.

The most important feature in the metabolism of iron (fig.3) is the degree to which body stores are conserved. Only about 10%, i.e., 1 mg/day of the total is lost per year by normal individuals. Two-thirds of this iron is excreted from the alimentary tract as extravasated red

cells, iron content in bile, and iron from the turn over of intestinal mucosal cells.

The remaining one third of iron los is accounted for by small amounts of iron in desquamated skin and in the urine. Physiological losses of iron in humans vary over a narrow range between 0.5 mg in the iron-deficient individual and 1.5-2 mg per day if excessive iron is consumed.

The limited physiological losses of iron shows the primary importance of intestinal iron absorption in determining the body's iron content[18]. Soon after acidification and start of digestion of food in the stomach, iron is presented to the intestinal mucosa as either inorganic iron or heme iron. An enzyme called ferrireductase, a duodenal cytochrome B located on luminal surface of absorptive cells of the duodenum and upper small intestine, transforms the iron from the trivalent ferric form into divalent ferrous state.

Ferrous iron forms the substrate for the *Divalent metal (ion) transporter 1 (DMT1).* The function of DMT1 is to transport the iron molecule to basolateral membrane of the intestinal epithelial cells. Here it is taken up by another transporter, ferroportin and again reoxidized to Fe^{3+}, primarily by *Hephaestin*. Hephaestin is a transmembrane copper-dependent ferroxidase enzyme. The resultant oxidized iron gets bounds to Apo-transferrin.

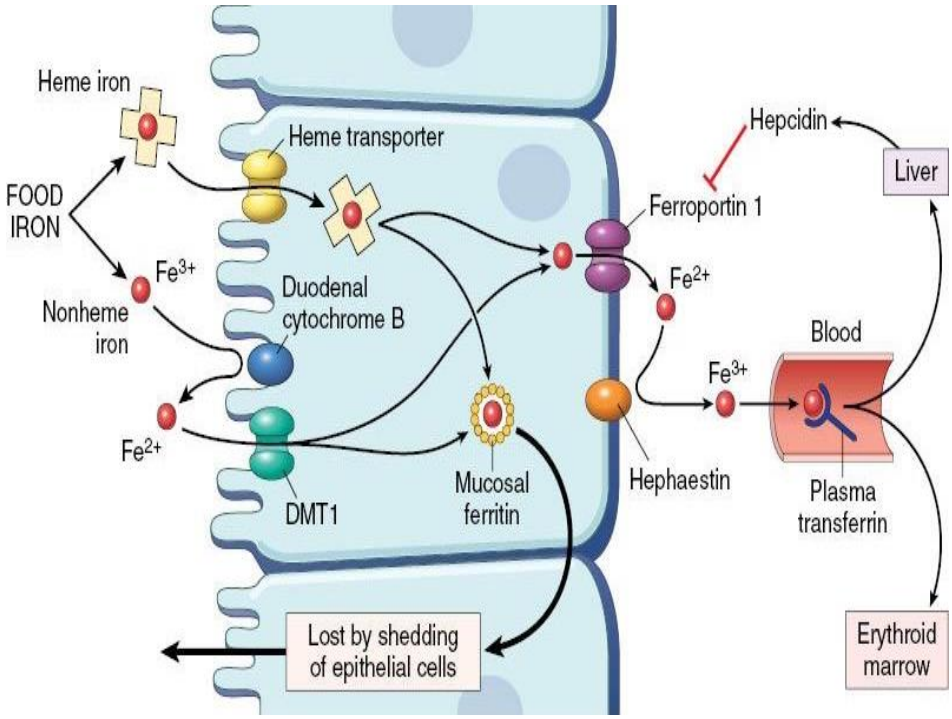


Figure 4: Mucosal absorption of Iron

Intestinal mucosal cell iron transport (fig.4) and the delivery of iron to transferrin from reticulo-endothelial stores are primarily determined by the human hemochromatosis protein. This is a protein belonging to major histocompatibility complex class 1 molecule encoded by the HFE gene.

The gene for HFE is located at the short arm of chromosome 6 at 6p21.3. Its expression is finely tuned to prevent iron overload during periods of body iron excess. Thus this allows for increased absorption as well as mobilization of iron stores during iron deficiency.

A predominant negative modulator of iron absorption in the duodenum is *Hepcidin***.** It is a 25–amino acid peptide chain synthesized by hepatocytes[19]. The production of hepatic hepcidin is greatly enhanced during inflammation or by iron overload states. A deficient hepcidin response to iron loading can contribute to pathological states of iron overload. This eventually leads to hemochromatosis.

In anemia of chronic disease, hepcidin production can be augmented by up to 100-fold. This explains the characteristic features of anemia in chronic disease, comprising of poor GI uptake and enhanced accumulation of iron in the reticuloendothelial system.

Iron Requirements and the Availability of Dietary Iron

Iron requirements are mainly determined by obligatory physiological losses and the needs imposed by growth (Tab.1). Thus periods of increased growth like infants may require up to 1.4 mg of iron daily.

Table 1: Age-wise requirement of iron

Age	**Iron RDA (*mg/Kg*)**	**Iron Bioavailability (*mg/Kg*) Poor Diet–Good Diet**	**Safety Factor *Available/Requirement***
Infant	67	33–66	0.5–1
Child	22	48–96	2–4
Adolescent (male)	21	30–60	1.5–3
Adolescent (female)	20	30–60	1.5–3

Obviously, infancy and preschool age represent periods of negative iron balance. The balance between dietary intake and body requirements is reflected by the size of iron stores. This is low or even absent when iron balance is adverse and high when iron balance is favorable. In most children after the third month of life and in preschool age groups, stores of iron are negligible.

In developed countries, an average diet contains 6 mg of iron per 1000 calories, thus fulfilling the an adequate daily iron intake. Animal meat such as liver and heart, yeast, egg yolks, oysters, wheat germ and certain dried beans and fruits constitute iron rich foods with high iron content of more than 5 mg/100 g.

Foods with low iron content i.e., <1 mg/100 g, are milk and milk products and most non-green vegetables. The content of iron in food also depends upon on the manner of its preparation, for example iron may be added from cooking in iron pots.

Even though the iron content of the food is important, much greater nutritional significance lies on the bioavailability of iron in food. Heme iron, which accounts to about 6% of total dietary iron intake, is far more bio-available. This is because this for is absorbed independent of the diet composition; Therefore it represents 30% of dietary iron absorbed.

But non-heme fraction of iron represents the largest amount of dietary iron ingested by the people in economically underprivileged. In a vegetarian diet, non-heme iron is absorbed poorly because of the inhibitory action of a variety of dietary constituents, particularly phytates and phosphates (fig.5).

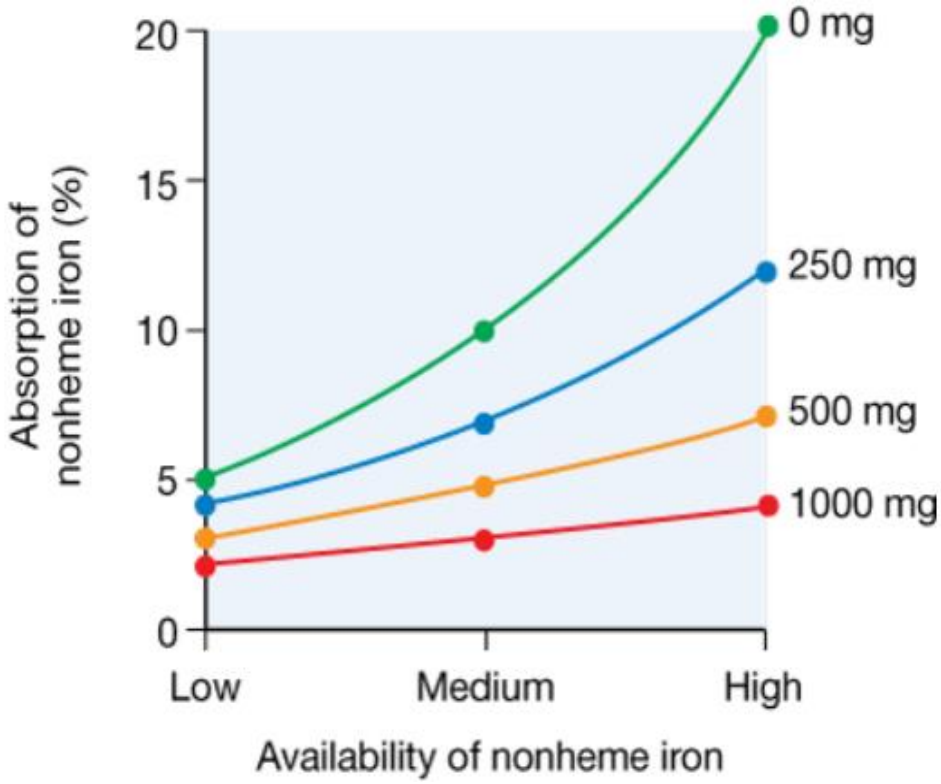


Figure 5: Absorption of Non-heme iron

Conversely ascorbic acid and meat increases the non-heme iron absorption. Particularly ascorbates forms complexes with ferric forms and reduces them to ferrous iron. Animal meat also facilitates the absorption of iron by increasing gastric acidity. Either of these substances can increase bio-availability of non-heme iron to several fold.

Iron Deficiency

Iron deficiency is the most common nutritional disorder[20]. In developing countries, up to 20-40% of infants and preschool children may be affected. Better iron balance can result from the practice of fortifying food stuffs, by the use of iron-fortified formulas for infants, and the prescription of iron supplements during pregnancy and childhood peroids.

Iron-deficiency anemia results from inadequate dietary intake of iron to meet normal requirements (nutritional iron deficiency), blood loss, or interference with iron absorption. This may be due to genetic disease, as in iron-refractory iron deficiency anemia where patients have iron deficiency that is refractory to oral iron therapy, but remain partially responsive to parenteral iron.

Acquired conditions can also cause poor oral absorption and can be associated with impaired oral absorption of vitamin B12 or following partial gastrectomy. More severe iron deficiency usually result from blood loss, either from the alimentary tract, or in through menstruation in women. Finally, treatment of patients with erythropoietin can result in a functional iron deficiency due to erythroid expansion.

Iron deficiency in infants and young children also lead to behavioral disturbances and can impair overall development. Some of

this disturbances may not be fully reversible. Iron deficiency in children can lead to an increased risk of lead intoxication secondary to pica as well as an excess absorption of heavy metals. Premature and low-birth weight infants are particularly vulnerable for developing iron deficiency, especially if they are not breast-fed or if fed on noniron-fortified formula. After the age of 2-3 years the requirement for iron declines gradually.

The recognition of iron deficiency depends up on an appreciation of the chain of events that lead to depletion of iron stores. Initially a negative balance results in a decrease of iron stores and eventually a parallel decrease in red cell iron and various other iron related enzymes.

In children the depletion of iron stores can be characterised by a low plasma ferritin (<10 ng/L) and the absence of reticuloendothelial hemosiderin in the marrow aspirate. Iron deficiency is also identified by a decreased saturation of transferrin below 16% and a raised red-cell protoporphyrin levels.

Iron deficiency anemia is characterized by a decrease in the hemoglobin concentration in blood. But the physiological variation in hemoglobin levels is so enormous that only about half the individuals with iron deficient erythropoiesis are identified from their anemia.

In mild iron deficiency, identifying the underlying etiology is more important than any symptoms related to the deficiency state. Because of the frequent incidence of iron deficiency in infants, the need for elaborate investigations of such individuals usually is determined by the severity of the anemia.

Although the presence of microcytic anemia is the most common indicator of iron deficiency, laboratory tests such as a decreased reticulocytic count and a low serum ferritin are essential to distinguish iron deficiency from other causes of microcytosis. Reticulocytic count and serum ferritin are particularly useful when circulating eryhtrocytes are not yet microcytic because of the recent nature of blood loss, but a low iron supply tend limits erythropoiesis.

Clinically it is more difficult to differentiate a true iron deficiency anemia from an iron-deficient erythropoiesis due to chronic inflammation. In the anemia of chronic disease, total body iron stores actually are increased, but the release of iron from reticuloendothelial cells is blocked. Here the plasma iron concentration is decreased, and the supply of iron to the erythroid marrow becomes inadequate. The increased stores of iron in this condition may be demonstrated directly by examination of an aspirate of marrow or may be seen in laboratory determination of an elevated plasma concentration of ferritin.

TREATMENT OF IRON DEFICIENCY

General Therapeutic Principles

The clinical response of iron deficiency anemia to therapy is influenced by several factors, including the severity of anemia, the ability of the patient to tolerate and absorb medicinal iron, and associated complicating illnesses.

Therapeutic effectiveness is best measured by the post supplemental increase in the rate of production of erythrocytes. The magnitude of the marrow response to hematinic therapy is directly proportional to the severity of the anemia and the amount of iron delivered to erythropoietic precursors.

The patient's ability to tolerate and absorb the orally administered iron is a key factor in determining the rate of response to therapy. The small intestine regulates absorption. As the doses of orally administered iron increases, entry of iron into the bloodstream gets limited. This provides a natural ceiling on dose of iron can be supplied by oral therapy.

In the patient with a moderately to severe iron deficiency anemia, tolerable doses of oral iron will deliver, at most, 20 – 30 mg of iron per day to the erythroid marrow. This is an amount sufficient for erythropoiesis to proceed at the rates of two to three times normal.

Co-existing medical illness also can interfere with the response of an iron-deficiency anemia to iron therapy. By decreasing the number of erythropoietic precursors, intrinsic disease of the marrow can blunt the response.

Any chronic inflammatory illnesses suppress the rate of red cell production, either by reducing iron absorption and reticuloendothelial release or by direct inhibition of erythropoietin and erythroid precursors. Continued blood loss can compromise the response to iron therapy as measured by recovery of the hemoglobin or packed cell volume.

Clinically, the effectiveness of iron therapy is best evaluated by assessing the an increasing reticulocyte count and the rise in the hemoglobin or the packed cell volume. An increase in the reticulocyte count is observed in 3-6 days after beginning therapy. A measurable increase in the hemoglobin level takes even longer peroid following initiation of iron therapy.

A decision about the effectiveness of iron should not be made within 3-4 weeks after the start of treatment. An increase of 1-2 g/dl in the concentration of hemoglobin by that time should be considered an adequate response, assuming that no other change in the patient's clinical status can account for the improvement and that the patient has not been transfused.

If the response to oral iron is inadequate, it is prudent to reconsider the diagnosis. A thorough laboratory workup should be conducted and poor compliance by the patient or the presence of a concurrent inflammatory disease must be looked. Concurrently any source of continued bleeding obviously should be sought. If these are found negative then an evaluation of the patient's ability to absorb oral iron should be considered.

It is not justified to merely continue with oral iron therapy beyond 3-4 weeks if a favorable response has not occurred.

Once a positive response to oral iron is demonstrated, therapy should be continued until the hemoglobin value gets normalized. Treatment may be continued if it is desirable to replenish iron stores. This may require a considerable period of time because the rate of absorption of iron by the intestine will fall remarkably as iron stores are restored.

The use of prophylactic oral iron should be reserved for patients at high risk of developing iron deficiency, including pregnant women, women with excessive menstrual blood loss and infants. Iron supplements also may be indicated in rapidly growing infants who are consuming substandard diets and for adults with a recognized cause of chronic blood loss.

Therapy with Oral Iron

Oral ferrous sulfate preparation is the treatment of choice for iron deficiency anemia. Ferrous salts are absorbed about three times better than ferric salts. This discrepancy becomes even greater at high oral dosages. Variations in the particular ferrous salt do not greatly influence bioavailability following oral administration.

The oral salts such as sulphate, fumarate, succinate, gluconate, aspartate, other ferrous salts, and polysaccharide ferrihydrite complex are absorbed to approximately the same extent. The effective dose of all of these preparations is based on their elemental iron content.

Other iron compounds have their role in fortification of foods stuffs. Reduced iron such as metallic iron and elemental iron are as effective as ferrous sulfate, if the preaparations used have small particle size. Large size of the particle such as ferrum reductum and salts of iron phosphate have a much lower bioavailability. When these are employed for the fortification of foods have been undoubtedly responsible for some of the confusion concerning effectiveness of food fortification.

Salts such as Ferric edetate has been shown to have good bioavailability. They additionally have advantages for maintenance of the normal appearance and taste of food upon food fortification.

The amount of elemental iron, rather than the mass of the total salt in iron tablets is important. It is also important that the coating of the tablet should dissolve rapidly in the stomach. Interestingly, because iron usually is absorbed in the upper small intestine, certain sustained release formulations have been reported to be as effective as uncoated tablets. They have been said to be even more effective than ferrous sulfate when taken with meals.

Numerous substances are designed to enhance the absorption of iron. They include surface-acting agents, carbohydrates, inorganic salts, amino acids and vitamins like ascorbic acid. When present in an amount of 200mg, vitamin C enhances the absorption of orally administered iron by at least 30%. However the enhanced uptake is associated with a significant increase in the incidence of adverse effects.

Therefore, the addition of ascorbic acid seems to offer little advantage over increasing the dose of iron administered. It is not advisable to use preparations that contain other compounds with intrinsic therapeutic actions of their own like Cyanocobalamine, Folate, or Cobalt

because the patient's response to the combination are difficult to interpreted.

The average therapeutic dose of iron for the treatment of iron-deficiency anemia is about 3-6 mg/kg per day. Children weighing 15-30 kg can take half the average adult dose; small children and infants can tolerate relatively large doses of iron i.e., up to 5 mg/kg.

The dose employed should be a balance between the desired therapeutic action and the adverse effects. Prophylaxis as well as mild nutritional iron deficiency may be managed with modest doses of oral iron. While treatment is the object, a dose of 2-3 mg/kg per day is employed.

The expected outcome for different dosage regimens of oral iron varies. These effects are influenced by the severity of the iron deficiency anemia and by other factors such as the time of intake of iron relative to meals. Bioavailability of iron taken with food is probably one-half or one-third of that observed in the fasting subject.

Antacids greatly reduce iron absorption if both are given concurrently. It is always preferable to administer iron in the empty stomach. In such conditions, even the dose may be reduced to lessen the gastrointestinal adverse effects.

Sustained high rates of erythropoiesis needs an uninterrupted supply of iron. The oral doses of iron should be spaced equally to maintain a adequate concentration of iron in plasma (Tab.2).

TOTAL DOSE OF IRON	**ESTIMATED ABSORPTION**		**INCREASE IN Blood Hb**
(mg/day)	**%**	**mg**	**(g/L/day)**
35	40	14	0.7
105	24	25	1.4
195	18	35	1.9
390	12	45	2.2

Table 2: Response to iron therapy.

The duration of treatment is influenced by the rate of recovery of hemoglobin and the target iron storage level. The former depends on the severity of the initial anemia. With a daily rate of replenishment of 0.2 g/dl of hemoglobin, the red-cell mass usually is normalized within 1-2 months. Thus an individual with a hemoglobin of 5 g/dl may achieve a normal complement of 15 g/dl in 50 days, while an individual with a hemoglobin of 10 g/dl may take only half that time.

The creation of stores of iron requires several months of oral iron therapy. The rate of absorption decreases dramatically soon after

recovery from anemia and by 3 - 4 months of treatment, stores may increase at a rate of not much more than 100 mg/month.

The plan of the strategy of continued therapy depends on the estimated future iron reserve. Patients with a diet inadequate in iron may require continued therapy with low doses of iron. If the bleeding has arrested, then further therapy is not required after the hemoglobin has returned to normal. With continued bleeding, long term, high dose iron therapy is indicated.

Untoward Effects of Oral Preparations of Iron

Intolerance to oral preparations of iron manly related to the amount of soluble iron in the upper GI tract. Psychological factors also play a role. Side effects include epigastric pain, nausea, upper gastric discomfort, heartburn and diarrhea or constipation.

It will be more acceptable to initiate therapy at a small dosage, to demonstrate freedom from adverse effects at that level and then gradually to raise the dosage to the desired level. With a dose of 200 mg of iron per day divided into three doses, symptoms occur in 25% of treated individuals vs 13% among those receiving placebo. This increases to about 40% when the dosage of iron is doubled.

Nausea and upper abdominal pain are more common at high dosage. Constipation and diarrhea, both related to iron-induced changes in the intestinal bacterial flora, are not more seen at higher dosage.

If a syrup formulation is used, one can place the iron solution on the back of the tongue with a dropper to prevent transient teeth staining.

The normal individual have the capacity to control absorption of iron despite high intake. Only individuals with underlying disorders that augment the absorption of iron have the hazard of developing iron overload hemochromatosis.

REVIEW OF LITERATURE

REVIEW OF LITERATURE

The initial concept regarding intermittent iron supplementation comes from studies on iron-deficient rats. In the iron deficient rats, the true absorptive and iron retention capacities for iron declined rapidly when iron was given on daily basis rather than on intermittent administration. These studies gave rise to many human studies that generally showed adequate efficacy compared with daily iron supplementation in terms of Hemoglobin levels and safe increments of iron reserves.

Beaton and McCabe[21], in an analysis of experiences with intermittent and daily iron, initially suggested that daily iron supplementation was superior to intermittent supplementation in pregnancy on the basis of Hemoglobin responses. Beaton later recognized that the original estimation of superiority of daily supplementation, if adjusted by the pregnancy stage at which the iron supplementation intervention started, essentially disappeared.

In 1958, *Bothwell et al.,* [22] published studies from which they concluded that both the size of iron stores and the rate of erythropoiesis influenced iron absorption in humans.

The theory behind intermittent oral iron supplementation was based initially on the concept of *a "mucosal block"* of iron absorption[23] . Early studies have shown that a single bolus of oral iron could inhibit the absorption of a test dose of radio iron given only a few hours later[24].

The rapid development of this refractory state, referred to as the "mucosal block," supported the notion of local regulation of iron absorption by the enterocyte and more particularly by its ferritin content[26]. Based on this theory argues that mucosal enterocytes down-regulate iron absorption in response to daily exposure to a high intake of iron. There is an increase in mucosal ferritin synthesis, an increase in the proportion of enterocyte iron that is stored in the cell, and a decrease in transfer of iron to transferrin in the vascular pool.

The current view is that hepcidin inhibits the release of iron from absorptive enterocytes and iron-recycling macrophages into the circulation by binding to and promoting the internalization and subsequent degradation of Ferroportin[26]. Iron is then stored in ferritin and lost when mucosal cells exfoliate.

Based on these observations, *Fernando E. Viteri et al.,*[27] showed the True absorption and retention of supplemental iron is more efficient when iron is administered intermittently rather than daily to iron-normal and iron deficient rats. In the study he observed a very rapid decrease in true iron absorption that takes place when a daily iron supplement equivalent to 10 times the normal intake is administered preceding two meals in rats trained to meal-feed twice daily.

This marked and rapid decrease is observed in both iron normal and iron-deficient rats, revealing the blocking effect of previous high iron intake and the effect of iron repletion on iron absorption thereby questioning the common daily iron supplementation practices in humans.

Outcomes of iron studies on rats lead to the suggestion that iron supplementation need not be given on daily basis, but can rather be given on weekly or twice weekly manner. In daily dose, the intestinal mucosal cells get saturated quickly and iron absorption decreases. As the turnover rate of these cells is 3 to 5 days, a biweekly dose may be as efficacious and more cost-effective.

Compliance might also improve because fewer doses of iron would be needed. This hypothesis has been supported by studies comparing the effectiveness of hemoglobin or hematocrit response, which was found to be similar regardless of whether supplementation was daily, weekly, or twice weekly[28].

Schultink W et al.,[29] studied the effect of daily vs twice weekly iron supplementation on iron status in preschool children with low iron status in a randomized double-masked field trial. A total of 87 Subjects were selected on the basis of their hemoglobin concentration being < 11 g/L in finger-prick blood, and were divided into two groups.

During the 8 weeks peroid one group received a daily supplement of 30 mg elemental iron, while the other group received 30 mg iron twice per week. A complete data set was obtained from 32 children in the group supplemented daily and from 33 children in the group supplemented twice weekly. Hemoglobin and serum ferritin increased significantly in both groups ($P < 0.001$). The difference in treatment effect between groups was not significant after correction for the initial hemoglobin concentration.

It is concluded that in preschool children with low iron status, twice weekly iron supplementation has an effect on iron status similar to that of daily supplementation. The major limitation of the study was a small sample size and a shorter period of intervention both compromises the power of the study.

James D Cook and Manju B Reddy[30] in their research titled *Efficacy of weekly compared with daily iron supplementation*, studied the iron absorption from 50 mg radiolabeled ferrous sulphate in 23 healthy female volunteer subjects divided into two groups. The first group

received a labeled ferrous sulphate supplement was given with water and in the second group it was given with a rice-based meal.

In both groups, absorption was measured in a randomized fashion twice in each subject, once with daily and once with weekly supplementation. Those tested for daily supplementation were given an iron supplement daily for 6 days before testing whereas those tested for weekly supplementation were given no iron for 6 days before testing.

When the labeled iron supplement was given with water only, absorption averaged 8.5% with daily and 9.8% with weekly administration compared with 2.3% and 2.6%, respectively, when given with food. The 13% lower absorption observed with daily administration in both groups was not statistically significant ($P > 0.20$). These results indicate that there is no significant absorptive advantage in giving iron less often than once daily.

Similarly, *Hallberg*[31] reiterated that there is no evidence that weekly supplementation better prevents iron deficiency because the fundamental argument in its favor, that daily supplementation causes a mucosal block, is not valid.

The controversy appears to have been put to rest by a meta-analysis by *Beaton and McCabe*[21] analyzed the outcome of intermittent iron therapy in the prevention of iron deficiency anemia in developing countries. This was done based on the systematic analysis of results of 22 completed studies on iron supplementation.

The outcome in the individual projects are catogorized into three groups: pregnant women, school-age children & adolescents and preschool children. The result concluded that that both daily and weekly iron therapy are equally efficacious in the prevention of anemia. But daily administration is found to be more effective than biweekly iron except in situations where supervision is feasible with weekly regimens and not with daily supplementation.

Binay Kumar Shah et al.,[32] compared the effectiveness of weekly vs daily iron and folic acid supplementation for control of anemia in adolescent Nepalese girls and concluded that weekly supervised therapy is a good alternative to daily iron and folic acid administration. Weekly therapy appears to be equally effective yet causes fewer adverse effects, improves compliance, and reduces the cost of supplementation.

Based on these studies WHO in its position statement on *Weekly Iron and Folic Acid Supplementation (WIFS) for Preventing Anemia*[33] , recommends a weekly supplementation iron in the form of ferrous sulphate where the prevalence of anemia is more than 20 %.

Study justification

Concluding from the above reviews, comparable efficacy of improvement in hemoglobin with both intermittent and daily iron therapy is seen in most studies. However most of the studies were done in adolescent girls and women of child bearing age.

Data on the efficacy of intermittent regimen supplementation of iron in preschool children is scarce. Therapeutic daily iron given for the treatment of iron deficiency anemia causes many undesirable adverse effects, leading to poor drug compliance.

Presently, prophylactic intermittent iron supplementation has been accepted except in antenatal programs, for which debate is ongoing. The biweekly dosage schedule takes advantage of the turnover time for intestinal mucosal cells in humans, which is 3 to 5 days, favoring the regulation of iron absorption and avoiding the daily exposure of an iron-rich environment to such cells.

METHODOLOGY

STUDY DESIGN: Interventional study

RANDOMIZATION METHOD : Lottery randomization technique.

STUDY PLACE :

Outpatient department and inpatient wards of Institute of Social Pediatrics, Government Stanley Medical College, Chennai 600 001.

STUDY PERIOD :

September 2014 to August 2015

ETHICAL CLEARANCE :

Approved by the institutional ethics committee.

STUDY SUBJECTS :

Children of age 6 months to 5 years with Iron deficiency anemia attending the study center.

SOURCE OF FUNDING : None.

CONFLICT OF INTEREST : None.

CASE DEFINITION:

Anemia[34] in the age group of 6 months to 5 years is defined as a reduction of the hemoglobin concentration (Hemoglobin < 11g/dL) or Red blood cell volume (Mean Corpuscular Volume < 70 uM[3)].

Iron deficiency anemia is characterized by the presence microcytic hypochromic anemia, low reticulocytic count and a low serum ferritin level (< 12 ng/ml).

INCLUSION CRITERIA:

Children of age group between 6 months to 5 years, attending the pediatric health services with clinical features of anemia and those show laboratory evidence of anemia will be enrolled for the study.

EXCLUSION CRITERIA:

1. Those children who are already on iron supplementation.
2. Those children who had blood transfusion during the past 3 months.
3. Children with severe anemia as defined as Hemoglobin of less than 7.0 gm/dL or those with complications of anemia were excluded.
4. Acute illness during the study or within the past one month
5. Those with chronic illness and ongoing blood loss.

Those with intolerable adverse effects due to iron therapy and failure to show adequate response will be excluded from the study at any point of time for further evaluation and treatment.

Children with anemia due to causes and those not showing adequate erythropoiesis on follow up will be excluded from the study and will be evaluated separately.

Sample size calculation:

To detect a mean difference of 1 g/dl hemoglobin between the intervention and control groups with 80% power and 5% significance, assuming a standard deviation of 2.0 g/dl; 63 subjects/group are required. Assuming a loss to follow-up of 20%, the final sample size is 70 subjects in each group.

Methodology:

1. Informed written consent is obtained from the parents to undergo the study.
2. Children are clinically screened for anemia by history and physical Examination.
3. Blood samples are collected under sterile aseptic precautions.
4. Blood samples for hemoglobin estimation, peripheral smear study, hematocrit, red cell indices were collected in 2ml K3 EDTA vacutainer tubes (*Yucca Tube^{TM}, Yucca diagnostics, India*).
5. Serum samples for serum ferritin estimation is collected in 2 ml vacutainer with clot activator(*Hemo Tube^{TM} , MB Lab Consumables, India*) and estimation done by ELISA method.
6. Automated cell counter (*Horiba ABX Cell counter, France)* is used for estimation of Hemoglobin, Hematocrit and red cell indices. Gross variations in results were manually tested by Cyanmet Hemoglobin method.
7. Peripheral Smear Study : Done using Leishman stain and studied by pathologist for morphological changes of iron deficiency anemia. Children with typical features of iron deficiency anemia like microcytic and hypochromic erythrocytes were enrolled for the study. Subjects with other causes of anemia like hereditary spherocytosis, megaloblastic anemia, hemolytic diseases like sickle

cell disease and thalassemia will be excluded from the study for further evaluation.

8. Reticlocyte Count **:** Done by Pathologist using Methylene Blue stain (NICE Reticulocyte Fluid ™). Blood samples collected in EDTA tubes were used for the study. Equal volume of reticulocyte count fluid is added to the anti-coagulated blood sample and incubated for 30 minutes. Then a smear is made is on a glass slide and the fraction of reticulocytes per 100 RBC estimated to give the Reticulocytic count. Reference values are provided in Tab.3.**Reference values**

Table 3: Reference value of hematological parameters.

PARAMETERS	**MEAN**	**LOWER LIMT**
Hemoglobin (g/dl)	12.5	11.0
Hematocrit (%) 0.5 – 1.9 years 2 – 5 years	 37 38	 33 34
MCV (uM^3) 0.5 – 1.9 years 2 – 5 years	 77 79	 70 73
Reticulocyte count	0.5 to 1.5 % of erythrocytes	
Serum Ferritin	10 to 60 ng / dl	

9. Iron Preparation: The drug used for intervention in both group is Ferrous sulphate and Folic acid syrup with each 1 ml containing Ferrous Sulphate IP 100 mg (equivalent to elemental iron 20 mg) and Folic acid IP 100mcg (Biogenetics Drugs Pvt. Ltd. India, procured by hospital pharmacy through Tamil Nadu Government supplies).
10. Ferrous sulphate is chosen as the preparation of iron since it cheaper than most other iron formulation and since it is the preparation used in National programmes, the result of the study can be directly extrapolated for further community interventions.
11. Children were weighed using electronic weighing scale at the start of the study and were prescribed 3 mg/kg of elemental iron – twice a week i.e., on Monday and Thursday for intermittent treatment group and everyday in Daily regimen group. Mothers are advised to give the drug one hour before or after the food and tea in order to improve the bioavailability of iron.
12. Deworming: All the children were dewormed with oral Albendazole, based on WHO recommendations[34] - 200 mg chewable tablets for children 1-2 years and 400 mg chewable tablets for children above 2 years. Chewable tablets are preferred to avoid the choking hazard due to the large size of the Albendazole tablet
13. The children with IDA are randomly allocated into Group A

(Controls) and Group B (Study group) by random lottery method.

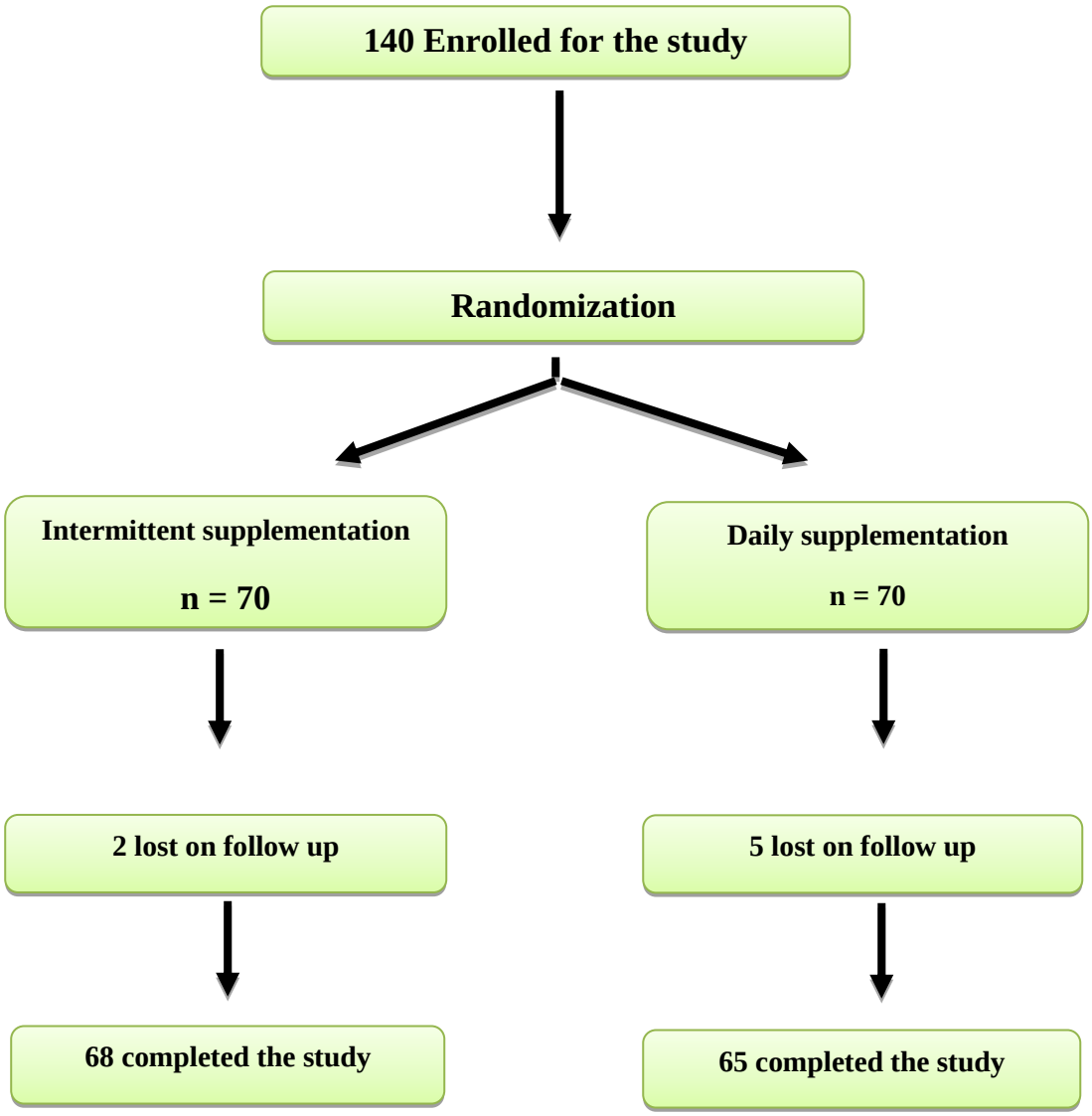
14. Children in Control group will receive 3 mg / kg elemental iron daily and those in Test group will receive the same twice weekly (Monday and Thursday) for 12 weeks.
15. Drug will be sourced from the Hospital Pharmacy. This includes Ferrous Sulphate syrup containing 100mg elemental iron per 5ml and albendazole 400mg chewable tablet.
16. Followed up at 3-5 days with reticulocyte count, at 4 weeks with hemoglobin and drug compliance and at 12 weeks for Hemoglobin and other red cell indices like PCV and MCV along with drug compliance and adverse effect assessment (using the checklist).
17. Management of adverse events: Mothers were informed about the possible adverse effects of ferrous sulphate and folic acid syrup and albendazole. Mothers were cautioned about accidental overdose with Iron syrup and the consequent serious toxicities. All mothers are instructed to bring the child to medical attention with any overdose of the prescribed medicines or untoward effects following the drug administration. Mothers are informed about the harmless nature of occasional black colored stools that may be seen in children on iron supplementation. The risk of teeth staining was explained. Any emergency medical issue will be attended in the 24 hrs pediatric casualty.

Statistical Analysis:

Intention-to-treat analysis will be followed to eliminate potential bias of excluding the subjects who do not comply or not available for follow-up. Data were in Microsoft excel sheets. Statistical analysis were done using IBM SPSS version 20.0 software package using computer. Methods included mean, standard deviation, Paired t test and Levene's test for equality of variances.

OBSERVATIONS AND RESULTS

Study design and follow up:



Out of the 140 children enrolled for the study (tab.4 & chart 4), 2 from the intermittent supplementation group and 5 from the daily supplementation group were lost on follow ups. Final reevaluation was done on 68 subjects in intermittent supplementation group and 65 subjects in daily supplementation group.

Table 4: Age- wise distribution of both study population before intervention

Age	Intermittent Regimen	Daily Regimen	Total
6 Months to 1 year	7	6	13
1 year to 2 years	19	19	38
2 years to 3 years	21	13	34
3 years to 4 years	8	19	27
4 years to 5 years	13	8	21

Final follow up evaluation included clinical examination and lab tests for estimation of hemoglobin, hematocrit, mean corpuscular volume

and serum ferritin assay. The age-wise distribution of the sample population is shown in table 1. The mean hemoglobin concentration and the number of subjects in each group appear to be similar in both the groups before intervention. (Tab. 5).

Table 5: Hemoglobin distribution of both study population before intervention

Hemoglobin g/dl	**Intermittent Regimen**	**Daily Regimen**
7 to 8	22	24
8 to 9	22	19
9 to 10	16	15
10 to 11	8	7

Table 6: Comparison of hematopoietic response of both study population at 3 – 5 days after iron therapy.

Parameters	Intermittent n=68	Daily n=65	p value
Retic Count			
Initial	1.24 +/- 0.35	1.16 +/- 0.34	
Final	2.16 +/- 0.25	2.57+/- 0.38	
change	1.03 +/- 0.42	1.40 +/- 0.47	p < 0.001

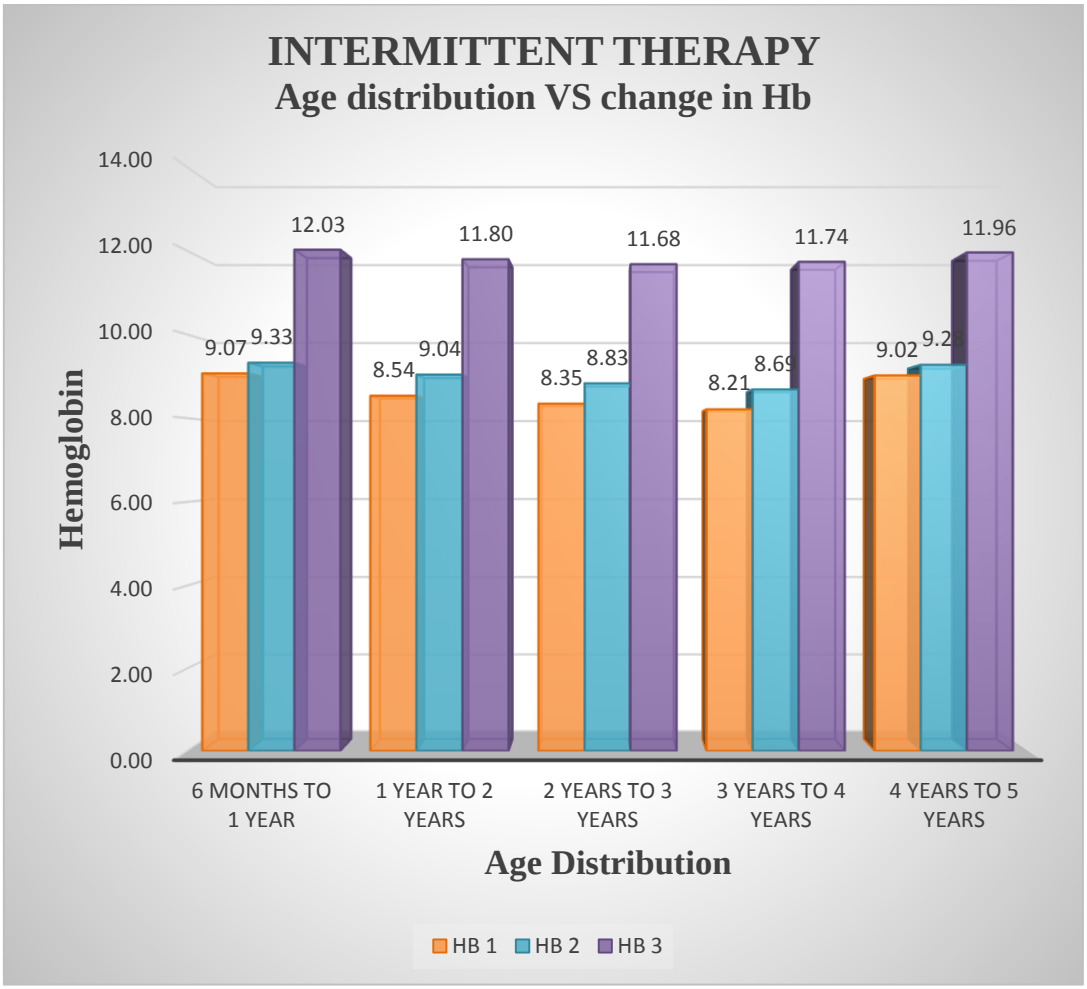
The initial mean reticulocyte count was 1.24 % of erythrocytes with a standard deviation of 0.35 %. The initial reticulocyte count of the daily iron therapy group was 1.16 +/- 0.34. The reticulocyte after 3-5 days in the intermittent and daily iron therapy groups were 2.16 +/- 0.25 and 2.57 +/- 0.38 respectively showing a significant reticulocytosis in both groups ($p < 0.001$). (tab. 6)

Table 7: Follow- up of Hemoglobin in Intermittent treatment group.

Age	Initial Hb	Hb at 4 weeks	Hb at 12 weeks
6 Months to 1 year	9.07	9.33	12.03
1 year to 2 years	8.54	9.04	11.80
2 years to 3 years	8.35	8.83	11.68
3 years to 4 years	8.21	8.69	11.74
4 years to 5 years	9.02	9.28	11.96

The age-wise improvement in hemoglobin concentration of children on intermittent iron therapy is shown in Table 7 and chart 2. This showed an uniform rise in hemoglobin in all age groups studied

Chart 2: Follow up of Hemoglobin in Intermittent treatment group.



Initial mean hemoglobin in the intermittent iron supplementation group was 8.58 g/dl with a standard deviation of 1.07 g/dl. The mean initial Hematocrit was 26.06 % with a standard deviation of 3.40. The mean initial mean corpuscular volume was 71.03 μM^3 with a standard deviation of 1.05 μM^3 . Initial serum ferritin was 10.18 ng/L with a standard deviation of 1.51 ng/L.

Table 8: Effect of Intermittent iron therapy on all hematological parameters.

Parameter	Initial	Final	Hemoglobin change Mean +/- SD	p value
Hemoglobin	8.58	11.81	3.22 +/- 0.75	< 0.001
MCV	71.03	77.78	6.75 +/- 1.69	< 0.001
Hematocrit	26.06	35.21	9.14 +/- 2.71	< 0.001
Serum ferritin	10.18	24.40	14.21 +/- 5.52	< 0.001

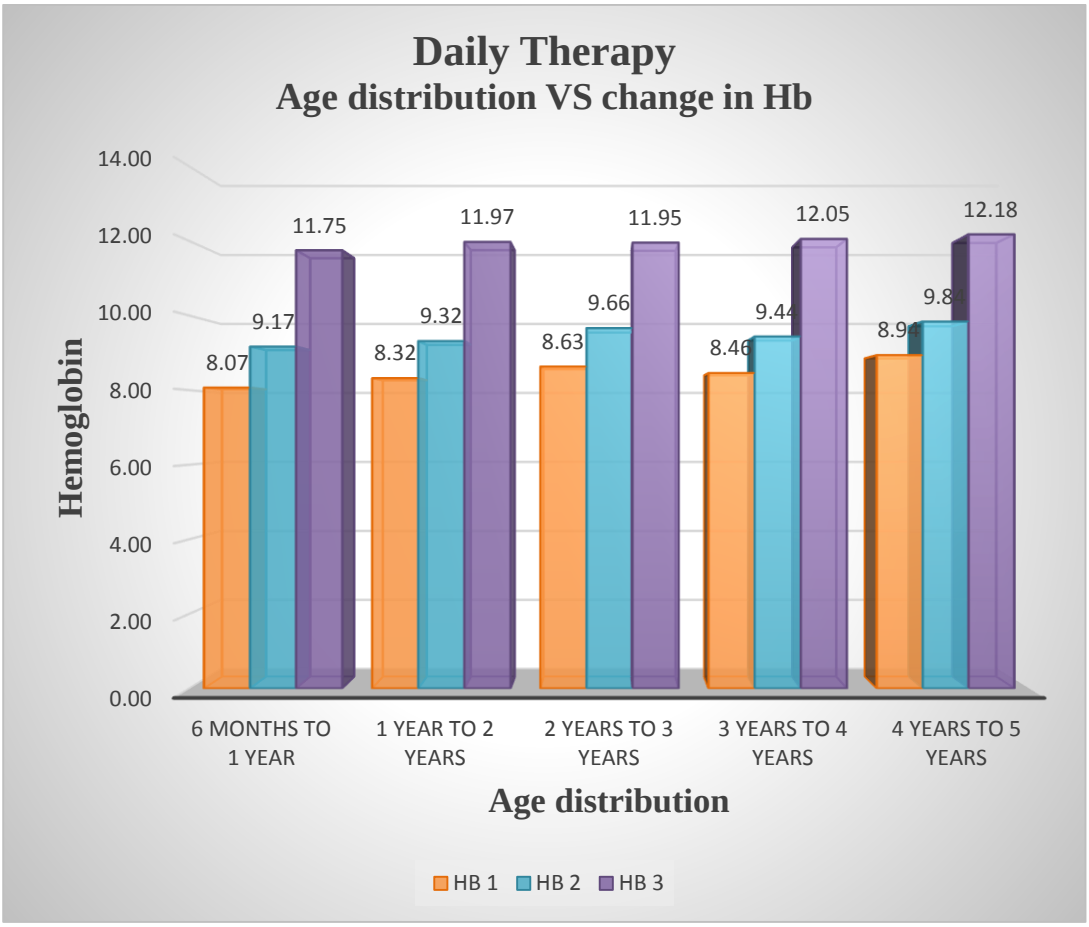
In the final assessment of intermittent iron supplementation group after 12 weeks, hemoglobin increased by a mean of 3.22 +/- 0.75 g/dL. Mean corpuscular volume increased by 6.75 +/- 1.69 uM^3, PCV increased by 9.14 +/- 2.71 % and serum ferritin increased by 14.21 +/- 5.52 ng/ml. The final increase was statistically significant with regards to all the variables (<0.001). (tab 8)

Table 9: Follow up of Hemoglobin in Daily treatment group.

Age	Initial Hb	Hb at 4 weeks	Hb at 12 weeks
6 Months to 1 year	8.07	9.17	11.75
1 year to 2 years	8.32	9.32	11.97
2 years to 3 years	8.63	9.66	11.95
3 years to 4 years	8.46	9.44	12.05
4 years to 5 years	8.94	9.84	12.18

The age-wise improvement in hemoglobin concentration of children on daily iron therapy is shown in Table 7 and chart 2. This showed an uniform rise in hemoglobin in all age groups studied.

Chart 3: Follow up of Hemoglobin in Daily treatment group



In the daily iron supplementation group, the initial mean Hemoglobin was 8.47 g/dl with a standard deviation of 1.01 g/dl (tab 9). The mean initial Hematocrit was 25.66 % with a standard deviation of 2.89. The mean initial mean corpuscular volume was 70.92 μM^3 with a standard deviation of 1.46 μM^3 .

The initial mean reticulocyte count was 1.16 % of erythrocytes with a standard deviation of 0.34 %. Initial mean serum ferritin was 10.11 ng/ml with a standard deviation of 1.65 ng/ml (shown in table 12).

Table 10: Effect of Daily iron therapy on all hematological parameters

Parameter	Initial	Final	Hemoglobin change Mean +/- SD	p value
Hemoglobin	8.47	11.99	3.52 +/- 0.78	< 0.001
MCV	70.92	77.72	6.80 +/- 1.88	< 0.001
Hematocrit	26.06	35.88	10.21 +/- 2.19	< 0.001
Serum ferritin	10.17	30.72	20.61 +/- 5.19	< 0.001

In the final assessment of daily iron supplementation group after 12 weeks, hemoglobin increased by a mean of 3.52 +/- 0.78 g/dL. Mean corpuscular volume increased by 6.80 +/- 1.88 uM^3, PCV increased by 10.21 +/- 2.19 % and serum ferritin increased by 20.61 +/- 5.19 ng/ml.

The final increase was statistically significant with regards to all the variables (<0.001). (tab 10)

Table 11: Comparison of follow up hemoglobin in both groups.

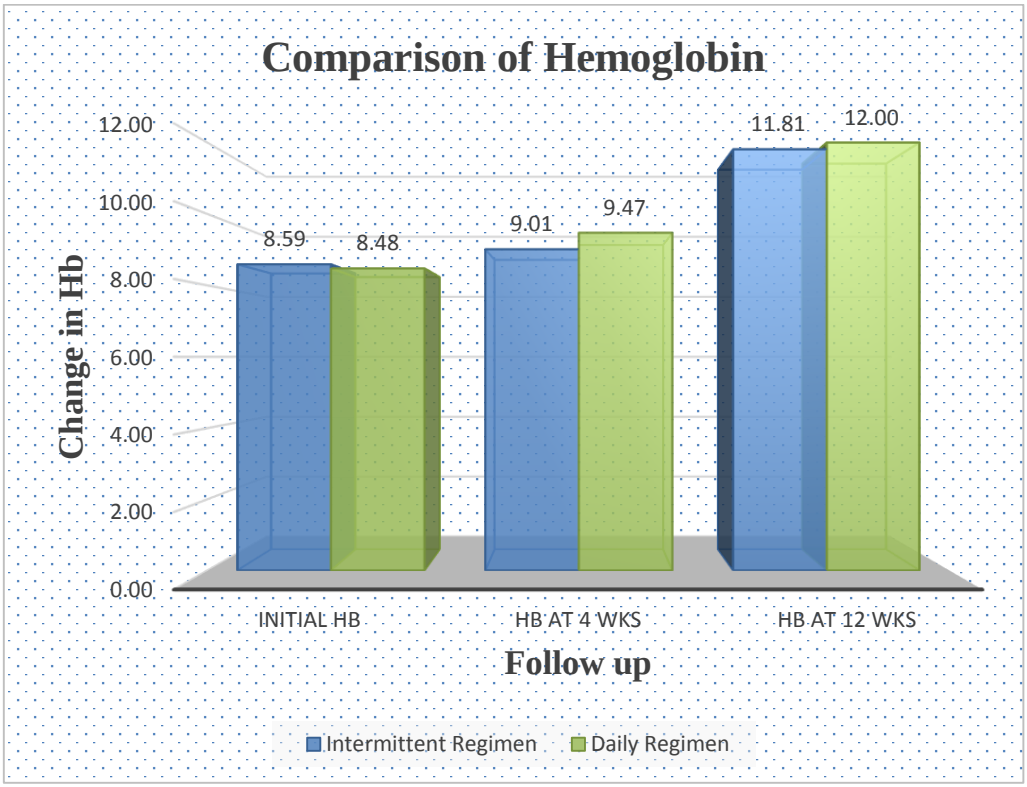
Category	Initial Hb	Hb at 4 wks	Hb at 12 wks
Intermittent Regimen	8.59	9.01	11.81
Daily Regimen	8.48	9.47	12.00

In the second follow up visit at 4 weeks, children in both groups were examined for clinical improvement of anemia, drug compliance and adverse events. Samples were taken for hemoglobin estimation.

The mean hemoglobin at the end of four weeks of intermittent iron supplementation was 9.01gm /dl with a standard deviation of 1.25 g/dl. The mean raise in hemoglobin observed was 0.43 g/dl.(Table 11). The mean hemoglobin after four weeks of intervention in daily

supplementation group was 9.47 g/dl with a standard deviation of 1.32 g/dl. The increase in mean hemoglobin was 1.0 g/dl. (Chart 3 & 4)

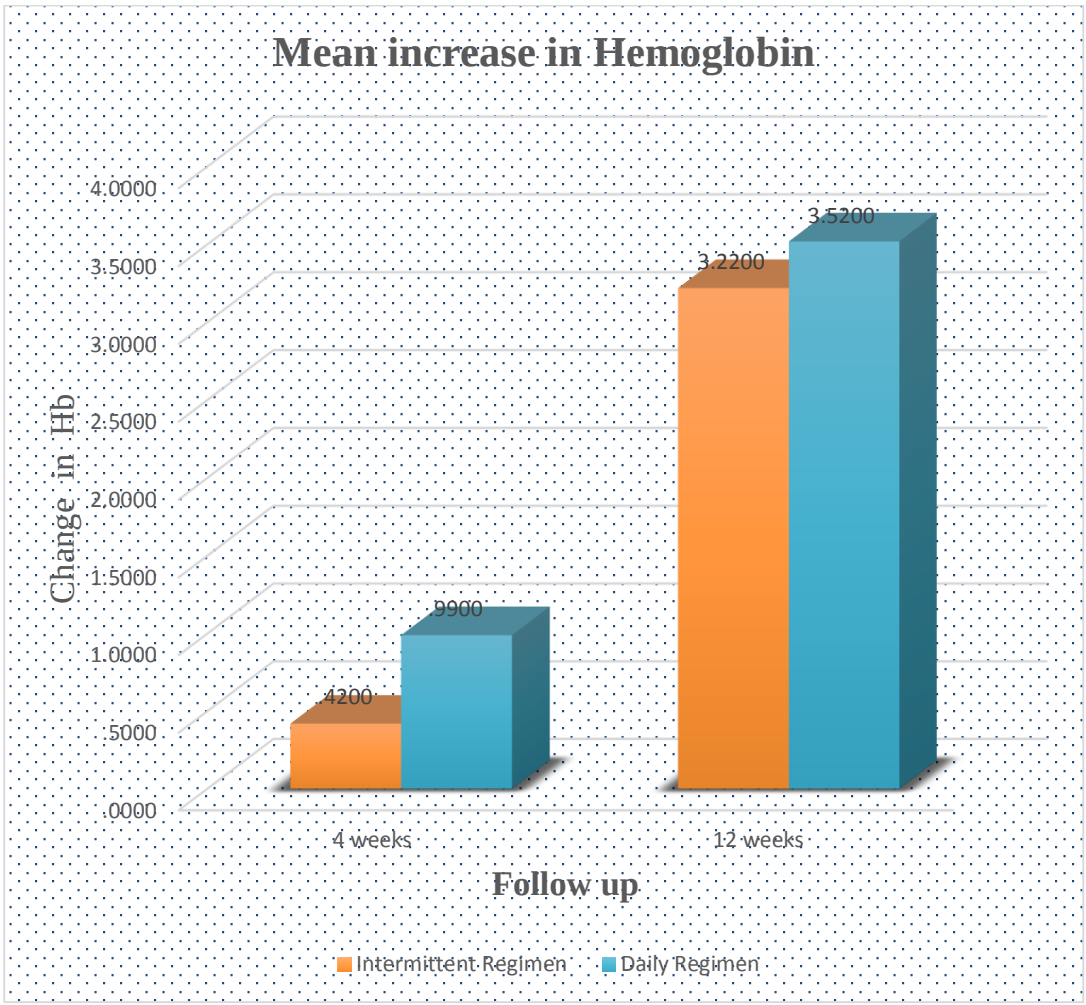
Chart 4: Comparison of follow-up hemoglobin both groups.



The mean hemoglobin at the end of four weeks of intermittent iron supplementation was 9.01gm /dl with a standard deviation of 1.25 g/dl. The mean raise in hemoglobin observed was 0.43 g/dl.(Table 11). The mean hemoglobin after four weeks of intervention in daily supplementation group was 9.47 g/dl with a standard deviation of 1.32 g/dl. The increase in mean hemoglobin was 1.0 g/dl. (Chart 3 & 4)

The study was completed after 12 weeks of iron supplementation and data collected from both intervention are analyzed using IBM SPSS statistical software version 20.0.

Chart 5: Mean increase in hemoglobin of both groups on follow up.



The final mean hemoglobin concentration for the intermittent group (n = 68) was 11.81 g/dl with a standard deviation of .45 g/dl. (Chart 5.) The mean final Hematocrit was 35.31 % with a standard

deviation of 1.52 %. The mean final mean corpuscular volume was 77.78 μM^3 with a standard deviation of 1.50 μM^3 . The final mean serum ferritin was 24.40 ng/ml with a standard deviation of 5.93 ng/ml.

Table 12: Comparison of hematological parameters of both groups.

Parameters	Intermittent n=68	Daily n=65	p value
Hemoglobin			
Initial	8.58 +/-1.07	8.47 +/- 1.01	
Final	11.81 +/- 0.45	11.99 +/- 0.44	
change	3.22 +/- 0.75	3.52 +/- 0.78	p = 0.190
MCV			
Initial	71.03 +/- 1.05	70.92 +/- 1.46	
Final	77.78 +/- 1.50	77.72 +/- 1.30	
change	6.75 +/- 1.69	6.80 +/- 1.88	p = 0.081
Hematocrit			
Initial	26.06 +/- 3.40	25.66 +/- 2.89	
Final	35.21 +/- 1.51	35.88 +/- 1.43	
change	9.14 +/- 2.71	10.21 +/- 2.19	p = 0.101
Ferritin			
Initial	10.18 +/- 1.51	10.11 +/- 1.65	
Final	24.40 +/- 5.93	30.72 +/- 5.33	
change	14.21 +/- 5.52	20.61 +/- 5.12	p < 0.001

In the final assessment of Daily iron supplementation group after 12 weeks, hemoglobin increased by a mean of 3.52 +/- 0.78 g/dL. Mean corpuscular volume increased by 6.80 +/- 1.88 uM^3, PCV increased by 10.21 +/- 2.19 and serum ferritin increased by 20.61 +/- 5.19 ng/ml. The final increase was statistically significant with regards to all the variables (<0.001). (tab 12)

Table 13: Comparison of adverse reaction in both treatment groups

S.No	Adverse effect	Intermittent treatment Group n = 68	Daily Treatment Group n = 65	p value (Significance)
1	Nausea	16 (23.5 %)	25 (39.6 %)	p = 0.032
2	Vomiting	8 (11.8 %)	11 (16.9 %)	p = 0.039
3	Dark stools	3 (4.4 %)	10 (15.4 %)	p = 0.033
4	Constipation	5 (7.4 %)	9 (13.8 %)	p = 0.023
5	Abdominal Pain	3 (4.4 %)	8 (12.3 %)	p = 0.048
6	Diarrhea	3 (4.4 %)	6 (9.2 %)	p = 0.269

The occurrence of adverse effects like nausea (p = 0.032), vomiting (p = 0.039), passing dark stools (p = 0.033), constipation (p = 0.023), abdominal pain (p = 0.048) were significantly more in the Daily supplementation group as compared to intermittent group. However the occurrence of diarrhea was similar in both groups. None of the study subject developed serious adverse reactions like anaphylaxis, diplopia or had encountered accidental poisoning.

The adverse effect profile in both the treatment groups are shown below. (chart 6 & 7).

Chart 6: Profile of adverse effects in Intermittent therapy Group

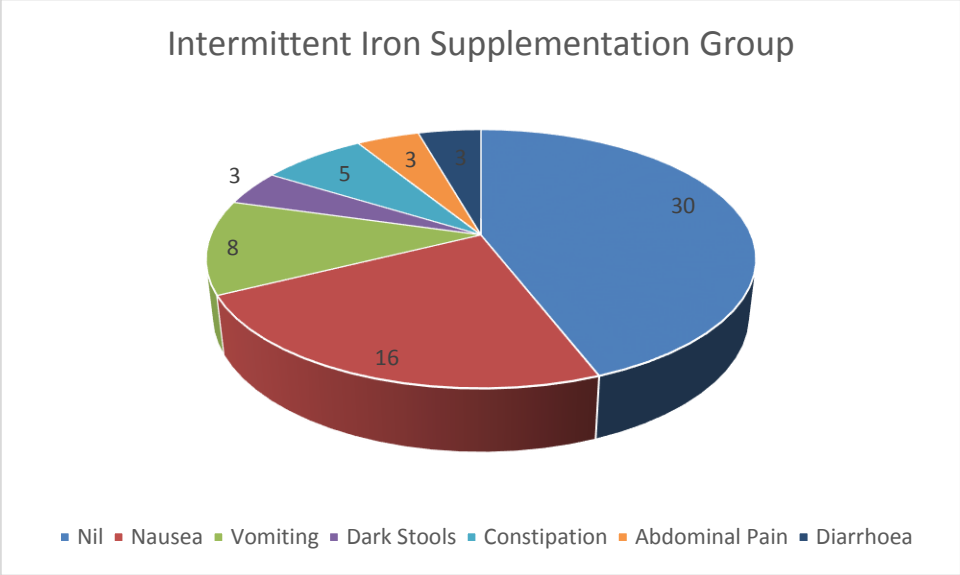
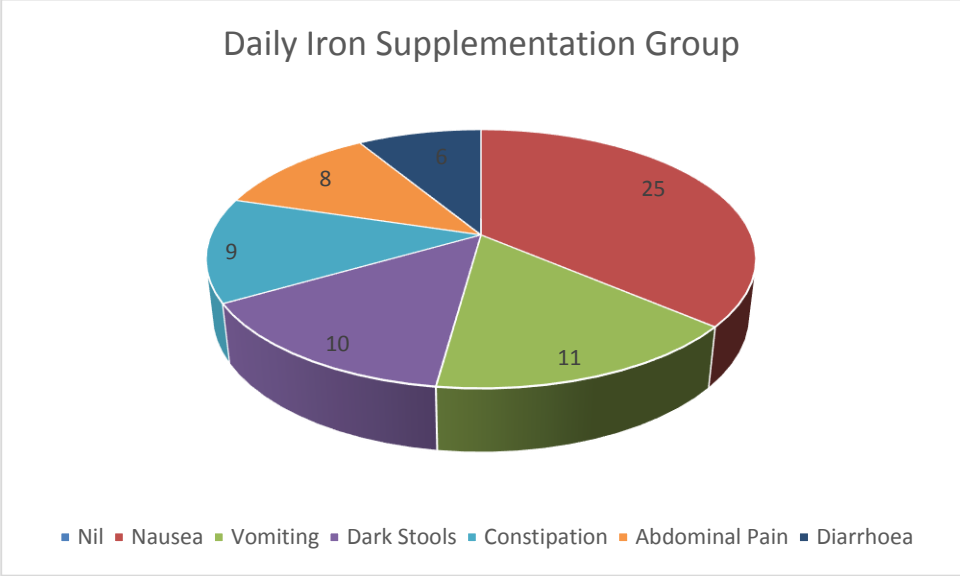


Chart 7: Profile of adverse effects in Daily therapy Group



DISCUSSION

In our Indian subcontinent, folic acid is routinely added to iron tablets in current national programs for control of anemia. Hemoglobin and Hematocrit levels in groups supplemented with daily and weekly iron and folic acid improved to an equal extent.

The characteristics of the both groups of study population were comparable in terms of mean age, gender and initial hemoglobin values.

A total of 68 out of 70 were able to complete the therapy with intermittent biweekly iron therapy whereas only 65 out of 70 completed therapy on daily therapy. Slightly improved patient acceptability is seen with intermittent supplementation group than with daily supplementation

There was no difference between the children who dropped out compared with those who continued in the trial in terms of age, initial

hemoglobin and serum. Similarly, there was no difference between the children who dropped out in the two treatment groups.

At the start of the study, there was no significant difference between initial hemoglobin concentrations of the two groups (mean initial Hb of 8.58 +/- 1.07 vs 8.47 +/- 1.01) although mean hemoglobin concentration of the daily group was marginally lower. Similarly, initial serum ferritin concentrations of the two groups did not differ (10.18 +/- 1.51 vs 10.11 +/- 1.65).

After an average 12 weeks of iron supplementation, there was a significant improvement in the hemoglobin concentrations in both groups. In the intermittent biweekly group there was an increase of 3.22g/dl of hemoglobin ($P < 0.001$); the comparative increase in the daily group was 3.53 g/dl ($P = 0.001$). **On comparison of the final hemoglobin values of both groups, there appears a slightly higher increase of hemoglobin in daily supplementation group. But the increase is not statistically significant (p = 0.190), thus showing that the outcome of both regimen appears similar.**

Similarly, the serum ferritin concentrations in the intermittent biweekly therapy group increased by 14.21 μg/L ($P < 0.001$), whereas in the daily supplementation group showed an increase of 20.61 μg/L ($P < 0.001$) . **Thus, serum ferritin has increased statistically significant in**

the daily group than in the intermittent biweekly group (p < 0.001).

In the present study, both intervention regimens of iron therapy (biweekly intermittent and daily) improved hemoglobin levels and the proportion of change from baseline to end of the intervention was found to be similar. Similar to our finding, Kotecha *et al.*, [35] in their study among adolescent girls in India reported that supervised once a week iron-folate administration (IFA) supplementation in schools was an effective intervention to reduce anemia. *Agarwal et al.* in their study on adolescent girls in India concluded that regular weekly iron-folic administration was effective and suitable for treating mild to moderate anemia.[36]

We observed that statistically significant increase in mean hemoglobin levels in the daily therapy than with intermittent therapy.

In our study**, the increment in serum ferritin was statically significant in the daily iron supplementation groups than with intermittent supplementation.** Similar to our finding, studies by Sungthong *et al*., [37] reported higher serum ferritin in school children receiving daily doses of iron than in those receiving weekly doses.

CONCLUSIONS

The result of this study has demonstrated that results of intermittent iron therapy have a similar response in increasing hemoglobin hematocrit and red cell indices like MCV compared to its daily administration, however the increase in serum ferritin was significantly better in the daily supplementation group. Further, biweekly administration of iron along with folic acid has improved drug compliance and fewer adverse reactions than with daily administration.

Hence it is concluded that intermittent (biweekly) iron therapy is an effective alternative to daily administration. A simple and inexpensive programs of biweekly iron supplementation can be used in

public healthcare clinics or at home to effectively reduce the prevalence of iron-deficiency anemia.

The results showed that the program of intermittent iron therapy described in this study fulfilled the requirements of providing easily administered iron supplementation involving minimal human resources at low cost and better drug compliance.

RECOMMENDATIONS

In developing countries, hematinic supplements are distributed through the primary health care systems. However, sustained efficacy is uncommon, owing to factors such as irregular tablet distribution and poor compliance. Thus less-frequent schedule would mean less cost and better compliance.

Hence we recommend that policy makers adapt intermittent regimens to tide over the major public health problem of iron deficiency anemia.

In infants and preschool children, biweekly supplementation through Anganwadi and RCH programs will lowers the prevalence of anemia in areas with high prevalence of the disease.

LIMITATIONS

1. The study is not double blinded.
2. The study was done using ferrous sulphate as the iron preparation. Hence the effect of other iron preparations cannot be extrapolated with this study.
3. Study is focused only on children of age 6 months to 5 yrs. Hence larger studies involving various age groups needs to be done.

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<u>சுய ஒப்புதல் படிவம்</u>

இரும்பு சத்து குறைபாடல் ஏற்படும் இராத்த சோகை நோய் சிகிச்சைக்கு, தினமும் மற்றும் இடைவிட்டு இரும்பு சத்து மருந்து கொடுக்கும் முறைகளை திறனை ஒப்பிடும் சோதனை.

ஆய்வாளர்: மரு.கிருஷ்ணகுமார் சின்னுசாமி

பட்ட மேற்படிப்பு மாணவர்

குழந்தை நலத்துறை

அரசு ஸ்டன்லி மருத்துவ கல்லூரி

சென்னை 600001

வழிகாட்டி: பேராசிரியர்: மரு. எஸ். இலக்ஷ்மி எம்டி, டிசிஎச்

குழந்தை நலத்துறை

அரசு ஸ்டன்லி மருத்துவ கல்லூரி

சென்னை 600001

பங்குபெரும் நோயாளின் விவரம்

பெயர்: வயது/பாலினம்:

மருத்துவமனை எண்:

இந்த மருத்துவ ஆய்வின் விவரங்கள் எனக்கு விளக்கப்பட்டது. எனது சந்தேகங்களை தீர்க்கவும் அதற்கான தகுந்த விளக்கங்களை பெறவும் வாய்ப்பளிக்கப்பட்டது.

நான் இந்த ஆய்வின் தனிச்சியாகதான் பங்கேற்கிறேன். எந்த காரணத்தினாலும் எந்த கட்டத்திலும் சட்ட சிக்கலின்றி இந்த ஆய்வின் இருந்து விலகிக்கொள்ளலாம் என்று அறிந்து கொண்டேன்.

நான் ஆய்வின் இருந்து விலகிக்கொண்டாலும் ஆய்வாளர் எனது மருத்துவ அறிக்கைகளை பார்ப்பதற்கோ அல்லது பயன்படுத்துவதற்கோ என் அனுமதி தேவைஇல்லை என்பதை அறிந்து கொண்டேன். என்னை பற்றிய தகவல்கள் ரகசியமாக பாதுகாக்கப்படும் என்பதை அறிவேன்.

இந்த ஆய்வின் மூலம் கிடைக்கும் தகவல்களும் பரிசோதனை முடிவுகளும் ஆய்வாளர் அவர் விருப்பத்திற்கேற்ப பயன் படுத்திக்கொள்ளவும் அதனை பிரசுரிக்கவும் முழு மனதுடன் சம்மதிக்கிறேன்.

இந்த ஆய்வின் பங்குகொள்ள சம்மதிக்கிறேன். எனக்கு கொடுக்கபட்ட அறிவுரைகளின்படி நடந்துகொள்ளவதுடன் ஆய்வாளருக்கு உண்மையுடன் இருப்பேன் என்று உறுதி அளிக்கிறேன்.

உடல்நலம் பாதிக்கபட்டால் அதனை தெரிவிப்பேன் என்று உறுதி அளிக்கிறேன். இந்த ஆய்வின் எனக்கு எந்த விதமான பரிசோதனைகளையும் சிகிச்சைகைக்கும் மேற்கொள்ள நான் முழு மனதுடன் சம்மதிக்கிறேன்.

இப்படிக்கு

நோயாளின் கையொப்பம் ஆய்வாளரின் கையொப்பம்

பெயர்

நோயாளின் தகவல் தாள்

இரும்பு சத்து குறைபாடல் ஏற்படும் இராத்த சோகை நோய் சிகிச்சைக்கு, தினமும் மற்றும் இடைவிட்டு இரும்பு சத்து மருந்து கொடுக்கும் முறைகளை திறனை ஒப்பிடும் சோதனை.

ஆராய்ச்சியின் நோக்கமும், ஆதாயங்களும்:

நம்மிடையே இரும்பு சத்து குறைபாடல் ஏற்படும் இரத்தசோகை நோய் அதிக அளவில் காணப்படுகிறது. இதை குணப்படுத்த கொடுக்கப்படும் இரும்பு சத்து மருந்து பக்க விளைவுகளை ஏற்படுத்துகிறது. இந்த மருந்திணை இடைவெளி விட்டு பயன்படுத்தும் போதும் தினமும் பயன்படுத்தும் பலனை அளிப்பதாக சில ஆராய்ச்சிகள் தெரிவிக்கின்றன. இது குழந்தைகளிலும் நிருபனம் ஆனால் அதிக பக்கவிழுவுகள் இன்றியும் எளிதாகவும் இந்த முறையை பயன்படுத்தி பலன் அடையாளம்.

ஆய்வு முறை:

இதில் உங்கள் குழந்தையின் குருதில், இரும்பு சத்து மருத்துவ சிகிச்சை கொடுப்பதற்கு முன்பும் பின்பும், இரத்தசோகை நோய்க்காண அளவீடுகளான ஹீமோகிலோப்பின், பெர்ரிடின் உட்பட அனைத்து தேவையான முக்கிய பரிசோதனைகள் செய்யப்படும்.

உண்டாகக்கூடிய இடர்கள்:

உங்கள் குழந்தையிடம் இருந்து மூன்று முறை 3 மிலி இரத்தம் எடுக்கப்படும். மேலும் இரத்தசோகை நோய்க்காண சிகிச்சைகாக இரும்பு சத்து மருந்து பரிந்துரைக்கப்பட்ட அளவில் பயன்படுத்தும் போது, வாந்தி, வயிர் எரிச்சல் போன்று அதற்குண்டான பக்கவிளைவுகள் ஏற்பட வாய்ப்புள்ளது.

ஆய்வில் உங்கள் உரிமைகள்:

உங்கள் மருத்துவ பதிவேடுகள் அந்தரங்கமாக வைத்துக்கொள்ளப்படும். இந்த ஆய்வின் முடுவுகள் அறிவியல் பத்திரிகைகளில் வெளியிடப்படலாம். இதில் உங்கள் பெயரோ அல்லது சொந்த தகவல்கள் வெளி வராது. ஆய்வில் பங்கேற்பது தனிசியானது மற்றும் காரணம் ஏதும் கூறாமலே நீங்கள் எப்போது வேண்டுமானாலும் விலகிக்கொள்ளலாம். எதுனும் பக்க விளைவுகள் ஏற்பட்டால் முழு சிகிச்சையும் மருத்துவ குழுவினரால் வழங்கப்படும்.

நாள் நோயாளின் கையொப்பம்

இடம் அல்லது இடது பெருவிரல் ரேகை

s.no	NAME	SEX	AGE	CAT	HB 1	RETIC 1	MCV 1	PCV 1	FERRI 1	RETIC 2	HB 2	HB 3	FERRI 3	MCV 3	PCV 3	Nausea	Vomiting	Dark stools	Constipation	Abdominal pain	Diarrhea
1	RAKESH	M	23	A	7.8	0.5	71	21	8.5	1.7	8.7	11.7	14.5	79	34	YES	no	no	no	no	no
2	POOJA	F	14	D	8.2	2.5	71	25	9	3.1	9.6	12.1	23	79	36	no	no	no	no	no	no
3	ARCHANA	F	36	D	10.8	1.3	72	31	12.5	2.65	11.2	12.5	32.5	77	37	no	no	no	no	no	no
4	KARTHICK	M	28	A	7.2	0.7	70	22	8.5	1.9	7.8	11.6	23	76	34	no	YES	no	no	YES	no
5	FARAHANA	F	43	D	9.6	1.2	72	28	11	2.3	10.3	12.1	33	77	36	YES	YES	no	no	no	no
6	IMARN	M	26	A	8.4	0.8	71	25	11	2.1	9.1	11.9	23.5	78	36	no	no	no	YES	no	no
7	KANIMOZHI	F	48	D	7.2	0.9	70	22	8	2.6	9.9	11.9	35	78	36	no	no	no	no	no	no
8	RANJITH	M	16	A	8.5	1.2	71	26	9.5	2.2	8.6	12.1	26	76	36	YES	no	no	no	no	no
9	PRIYA	F	12	A	10.2	0.8	72	32	12	2	10.2	12.6	22	76	37	no	no	YES	no	no	no
10	RAMESH KRISHNA	M	17	A	7.9	0.9	72	24	9	2.1	8.1	11.8	26.4	78	35	no	no	no	no	no	no
11	ANJALI	F	49	D	8.3	0.85	71	25	8	3.1	9.3	11.9	45.5	77	36	no	no	no	no	no	no
12	RESHMA	F	34	D	9.7	0.75	71	28	9.5	3.2	10.7	12.2	26	76	37	no	no	no	no	no	no
13	ARUN	M	56	D	7.2	0.6	69	23	8	2.1	9.2	11.8	27	79	35	YES	no	no	YES	no	no
14	FARHANA	F	21	A	9.8	1.2	71	30	11.5	2.3	10	12.3	26	80	37	no	YES	no	no	no	YES
15	PRATHISH	M	17	A	7.1	1.3	69	22	9	2.5	8.6	10.8	14	75	32	YES	no	no	no	no	no
16	MRITHULA	F	38	A	8.6	1.1	70	26	11	2.05	8.7	12	21	79	36	no	no	no	YES	no	no
17	MUSHARAF	M	42	D	9.4	0.75	71	28	11	2.4	10.3	12.4	28.5	77	37	no	no	no	no	no	no
18	IMRAN	M	27	D	7.3	1.2	71	22	8	2.1	9.9	11.6	31	76	35	no	YES	no	no	no	YES
19	KAMALESHWARI	F	7	A	10.6	0.6	72	32	12	1.8	10.7	12.8	31.5	76	33	no	no	no	no	no	no
20	SANJAY	M	31	D	8.3	1.5	72	26	10.5	2.2	10.4	11.9	32.5	79	36	no	no	YES	no	no	no
21	SARANYTA	F	52	A	7.9	0.95	71	23	10	2.1	8.1	11.4	28	78	34	no	no	no	no	no	no
22	POOJA	F	18	D	9.2	1.7	72	29	11	2.5	10.6	12.1	28	77	36	YES	no	no	no	no	no
23	ELAMRAN	M	60	A	8.7	0.75	72	25	9.5	2.3	8.8	12.1	22.5	76	36	YES	no	no	no	no	no

24	SEETHA	F	35	D	7.3	1.3	70	23	9	2.1	8.9	11.8	31	77	35	no	no	no	no	no	no
25	ELUMALAI	M	53	D	10.4	1	73	31	12.5	2.35	11.2	11.7	25	78	35	no	YES	no	no	no	no
26	RAJESH	M	22	D	7.2	1.2	71	22	7.5	2.6	8.6	11.8	23	77	35	YES	no	no	YES	YES	YES
27	HASINI	F	47	A	8.8	0.65	72	25	9	2.6	8.9	12.3	22	80	37	no	YES	no	no	no	no
28	SUDHA	F	36	A	7.4	1.25	71	23	8	2.1	8.4	11.6	19.5	79	34	no	no	no	no	no	no
29	AJAY	M	16	D	9.6	1.3	72	29	11	2.5	9.9	12.3	43.5	79	37	no	no	YES	no	no	no
30	VASANTHI	F	41	D	8.1	1.5	71	26	10	2.9	8.9	12.1	33	78	36	YES	no	no	no	no	no
31	KATRTHIKA	F	18	D	7.5	1.6	71	23	9.5	2.1	8.8	11.3	30	77	34	no	no	no	no	no	no
32	DHIYA	F	11	A	7.1	1.2	68	22	8.5	2.3	8.2	10.6	14	78	31	no	no	no	no	no	no
33	VIJAY	M	32	D	8.4	1.7	70	25	10	3.2	9.2	11.8	28.5	79	35	YES	no	no	no	no	no
34	KISHORE	M	51	A	9.3	0.8	71	30	11	2.95	9.4	12.2	24.5	76	37	YES	no	no	no	YES	no
35	SRIJA	F	14	D	8.4	1.5	70	25	11.5	2.1	9.3	12.4	32	79	37	no	no	YES	no	no	no
36	TIRUPATHI	M	44	A	7.2	0.9	69	22	8	2.1	8.6	11.9	19	80	36	no	YES	no	no	no	no
37	ARUNA	F	19	D	10.2	1.2	72	31	12	2.55	10.8	12.4	29	77	37	no	YES	no	no	no	no
38	SAMEER	M	59	A	8.3	0.75	72	24	9.5	2.15	8.3	11.8	21.5	75	36	no	no	no	no	no	no
39	SANGEETHA	F	9	A	9.7	0.6	72	30	12	1.95	8.8	12.3	27	79	37	YES	no	YES	no	no	no
40	KANNAN	M	16	D	7.3	1.3	70	22	13	2.85	8.8	11.3	43.5	78	34	YES	no	no	YES	YES	no
41	VIDHYA	F	58	A	9.4	0.85	72	29	11.5	2.1	9.5	12.2	34.5	79	37	no	no	no	no	no	no
42	RADHA	F	29	A	7.8	0.7	70	24	9	2.1	8.2	11.8	16	76	36	no	YES	no	no	no	no
43	MALA	F	39	D	8.2	1.5	71	25	9.5	3.1	9.2	12.3	35	79	37	no	no	no	no	no	no
44	ARULKUMAR	M	54	D	7.7	1.2	69	23	7	2.85	8.4	11.7	15	78	35	YES	no	no	no	no	YES
45	TRISHA	F	20	A	8.6	0.85	71	26	10	2.15	8.7	12.2	28.5	79	37	YES	no	no	no	no	no
46	SAKTHIVEL	M	19	A	10.2	0.95	72	31	12.5	2.35	10.3	12.4	26	78	37	no	YES	no	no	no	YES
47	KUMARAN	M	35	D	8.3	0.8	71	25	10	2.9	8.5	12.1	31.5	79	36	no	YES	no	no	no	no
48	ABIRAMI	F	28	A	7.2	1.5	69	22	8	2.1	8.2	11.2	19	80	34	no	no	no	no	no	no
49	KARTHICK	M	57	A	9.4	1.2	72	30	13.5	2.25	9.5	12.1	30	80	36	YES	no	no	no	no	no

50	SANMATHI	F	30	A	8.4	1.7	70	25	10	1.95	8.5	11.6	28.4	75	34	no	no	YES	no	no	no
51	SUPRIYA	F	45	D	7.1	0.95	70	21	7.5	2.1	8.2	10.8	26	76	31	YES	no	YES	no	no	no
52	KALAIYARASI	F	10	A	8	1.4	70	24	10	2.1	8.5	12.1	34	76	36	no	YES	no	no	no	no
53	KAMILL	M	20	D	7.9	0.75	70	24	11	2.3	8.6	11.7	33.5	78	35	no	no	no	no	no	no
54	JAYANTHI	F	16	D	10.2	0.95	71	31	12	2.1	10.7	12.9	31.5	79	39	no	no	no	no	no	no
55	AJEEZ	M	22	A	7.5	1	70	23	8.5	2.3	8.2	11.3	15	76	34	no	no	no	YES	no	no
56	HARINI	F	50	A	10.7	1.2	73	32	12	2.5	10.9	12.5	33	78	37	YES	no	no	no	no	no
57	KARTHICKUMAR	M	44	D	8.4	0.9	80	26	10.5	2.6	9.2	12.4	31	79	37	YES	no	no	no	YES	no
58	MURALI	M	37	A	9	1.4	70	28	10.5	2	9.5	11.9	19.4	77	36	no	YES	no	no	no	no
59	SRIPRIYA	F	20	A	7.6	1.9	69	23	8	2.85	8.4	11.8	21	79	35	no	no	no	no	no	no
60	MOHAN	M	41	D	9.1	0.85	71	28	11	2.3	9.5	12.6	29	80	38	no	YES	no	YES	no	no
61	ANADHI	F	8	D	7	0.9	68	22	7.5	2.65	8.3	10.7	28	77	32	YES	no	YES	no	no	no
62	CHANDER	M	14	A	8.3	2	71	25	12	1.2	8.7	11.6	21.5	78	35	YES	no	no	no	no	no
63	MEENA	F	36	D	9.3	1.2	70	28	10	2.35	9.9	11.8	34.5	76	35	no	no	no	no	no	no
64	JEEVAN	M	52	D	10.1	1.3	71	30	12.5	2	10.5	13.1	39	79	39	YES	no	no	no	no	no
65	VIGNESH	M	34	A	8.3	1.2	71	24	12.5	1.9	8.6	11.7	20	79	35	no	no	no	no	YES	no
66	NIRANCHANA	F	17	D	7.4	1.4	71	22	7	3.45	7.9	11.9	33	80	36	no	no	no	no	no	no
67	MAGESH	M	50	A	9.4	1.3	72	29	11	2.1	9.8	12.1	29.5	77	36	no	no	no	no	no	no
68	BALA	M	33	D	7.6	1.6	71	23	8	2.2	8.2	11.6	29	79	35	no	YES	no	no	no	no
69	LEELA	F	49	D	8.7	0.75	71	25	9.5	2.65	9.7	12.4	34.3	78	37	YES	no	YES	YES	YES	no
70	VINOD	M	19	A	7.2	1.25	71	23	8	2.2	7.7	11.2	21	77	33	YES	no	no	no	no	no
71	ARCHANA	F	43	D	10.3	0.95	72	31	12	2.45	10.9	12.6	26	79	38	no	no	no	no	no	no
72	SUGASINI	F	19	D	8.2	1.2	71	25	9	2.1	9.3	12.1	39	76	36	no	YES	no	no	no	no
73	JEGAN	M	42	A	7.6	0.75	71	23	9	1.9	8.1	11.4	21	78	34	no	no	no	no	no	no
74	REKHA	F	15	D	9.2	1.3	71	28	9	2.7	10.3	12.3	28.5	77	37	no	no	YES	no	no	YES
75	SATISH	M	54	A	8.5	0.85	72	26	10.5	1.85	8.9	11.9	14	79	36	no	no	no	no	no	no

76	PRATHIBA	F	20	D	7.8	1.3	71	24	7.5	2.55	8.9	11.4	29	76	34	YES	no	no	no	no	no
77	VIDHYA	F	45	D	8.9	1.4	72	27	9	3.1	9.9	11.9	31.3	75	36	no	no	no	no	no	no
78	CHRITOPHER	M	25	A	7.6	1.2	71	23	9	2.15	8	11.4	22.5	79	34	YES	no	no	no	no	no
79	NAVEEN	M	7	A	9.7	1.3	71	29	9.5	2.1	10.2	12.1	29	80	36	no	no	no	YES	no	no
80	NIMMY	F	21	D	8.3	1.5	71	26	9.3	2.85	9.4	12.4	28	75	37	no	YES	no	no	YES	no
81	PERUMAL	M	12	D	7.3	1.25	70	23	7.4	2.7	8.4	11.8	30	78	35	YES	no	YES	YES	no	no
82	RESHMA	F	54	A	8.4	1.45	71	25	10	2.3	8.7	11.9	19	77	36	no	no	no	no	no	no
83	NIRMAL	M	30	A	7.1	1.75	69	21	10	2.45	7.9	10.7	15.5	78	31	YES	no	no	no	no	no
84	FATHIMA	F	16	A	10.3	1.3	73	31	12.5	2.1	10.7	12.5	34	79	37	no	no	no	no	no	no
85	SULTANA	F	54	A	8.2	0.9	72	24	10	2	8.7	11.6	22.5	77	35	no	no	no	no	no	no
86	KATHIR	M	38	D	7.9	1.55	70	23	9	2.35	9.1	12.1	31.5	78	36	YES	no	no	no	no	no
87	MUTHU	M	27	A	9.8	0.75	72	31	11	2.3	10.3	11.9	19	78	36	YES	no	no	no	no	no
88	JESSICA	F	24	A	7.1	0.85	72	22	9.5	2	7.7	11.3	22	79	34	no	no	no	no	no	no
89	MARY	F	41	D	8.3	0.6	70	24	10	2.6	9.3	12.4	36	77	37	no	YES	no	no	no	no
90	SARAVANAN	M	52	D	10.4	0.8	72	31	12.5	2.8	11.1	12.9	31	79	39	YES	no	no	no	no	no
91	LAKSHMI	F	25	A	9.7	1.35	71	30	12	1.9	9.5	12.2	33	78	36	YES	no	no	no	no	no
92	ISAC	M	32	A	7.3	1.2	71	22	7	2.1	7.5	11.1	15.5	79	33	no	no	no	no	no	no
93	PREETHI	F	50	D	8.7	0.75	71	26	11.5	2.45	9.3	11.9	29.4	75	36	no	no	no	no	no	no
94	ISHWARYA	F	11	D	9.2	0.55	70	28	12	2.1	9.9	11.8	34	78	35	no	YES	no	no	YES	no
95	MUMTAJ	F	44	D	7.8	0.8	70	23	7	2.9	8.6	11.9	26	78	36	YES	no	YES	YES	no	no
96	VIVEK	M	20	A	8.4	1.6	71	25	10	2.3	8.9	11.8	25	79	35	no	no	no	no	no	no
97	POOJITHA	F	24	A	9.9	1.2	72	30	9.3	1.9	10.3	12	34	80	36	no	no	no	no	no	YES
98	FYAZ	M	47	D	7.3	0.9	69	23	10.5	2.75	8.4	11.8	21.5	77	35	no	no	no	no	no	no
99	ISABELL	F	60	A	10.8	1.35	73	33	12	1.85	11.2	12.2	37.5	78	36	no	no	no	YES	no	no
100	RAKESH	M	27	A	7.3	0.95	71	23	8	2.1	7.9	11.6	29	77	34	YES	no	no	no	no	no
101	HARITHA	F	19	D	8.2	1.2	70	25	11	2.45	9.3	12.7	32	76	37	YES	no	no	no	no	no

102	CHELLADURAI	M	10	D	7.9	1.2	70	24	11	2.1	9.1	12.1	36	78	36	no	no	YES	no	no	no
103	ARTHI	F	34	A	8.8	0.8	72	27	12	2.25	9.3	11.9	30	76	36	no	no	no	no	no	no
104	SUBAHSINI	F	36	D	9.1	1.3	71	27	12.5	2.1	10.1	11.9	32.6	75	35	YES	no	no	no	no	YES
105	MANOJ	M	18	D	7	1.4	70	21	10.4	2.6	7.7	11.2	21.5	78	33	no	no	no	YES	no	no
106	SRIVARSHAN	M	13	A	9.3	1.35	72	28	11	2.1	9.7	11.8	23	79	35	no	no	no	no	no	no
107	KANISHA	F	42	D	8.6	0.9	71	26	12	2.7	9.7	12.1	26	76	36	no	no	no	no	no	no
108	SINDHUJA	F	28	A	7.1	1.75	69	21	7.5	2.35	7.6	10.8	32.5	75	32	no	no	no	no	no	no
109	NISHANTH	M	25	A	10.6	1.25	71	32	12	2.3	10.9	12.1	27.5	78	36	no	no	no	no	no	no
110	BHARGAVI	F	38	D	9.3	0.85	71	29	11.5	2.1	10.2	12.4	26	79	37	YES	no	no	no	no	no
111	AMALA	F	8	D	9.8	0.75	72	30	12	2.5	10.6	12.3	37	78	37	no	no	no	no	YES	no
112	KAMALESH	M	24	A	8.2	1.4	71	25	11	2.4	9.2	11.6	29	78	35	no	no	no	no	no	no
113	ANUPRIYA	F	17	D	7.7	0.8	71	23	10	2.45	8.6	11.6	28	79	35	no	no	no	no	no	no
114	EDWIN	M	48	A	9.4	1.7	71	29	12	2.3	9.9	11.9	22	79	36	no	no	no	no	no	no
115	ARUNTHAMIL	M	32	A	8.6	1.2	71	26	10.5	2.1	8.9	11.7	26	79	35	no	no	no	no	no	no
116	ANUSHA	F	18	A	10.4	0.8	72	32	12	2.5	10.7	12.1	27.5	80	36	no	no	no	no	no	no
117	MULLAI	F	37	A	7.2	0.65	70	23	7	2.1	7.4	11.1	28	76	33	no	no	no	no	no	no
118	KUMARESH	M	29	A	9.7	1.4	71	30	11	2.5	9.7	11.8	22.5	77	35	no	no	no	no	no	no
119	RAGHU	M	43	D	8.3	1.25	72	25	12.5	3.85	9.2	11.6	29.7	77	35	YES	no	no	no	no	no
120	KANIMOZHI	F	25	D	9.6	1.6	71	29	11.5	2.9	10.6	12.3	37	78	37	no	no	no	no	YES	no
121	AMNURADHA	F	35	D	7.4	1.3	70	23	10	2.65	8.2	11.8	25	79	36	YES	no	no	no	no	no
122	PRABHA	F	12	A	8.2	0.7	71	24	11.5	2.1	8.7	11.7	21	75	35	no	no	no	no	no	no
123	HARSHINI	F	26	D	9.1	1.2	70	27	11	2.7	9.8	12.1	35	80	36	no	no	no	no	no	no
124	BALAGI	M	48	D	7.6	1.45	71	23	10.5	2.1	8.3	11.7	23.5	77	35	no	no	no	no	no	no
125	AKILA	F	60	A	8.3	0.85	71	26	10	2.6	8.8	11.5	28.5	76	34	no	no	no	no	no	no
126	JAYASANKAR	M	30	A	9.2	0.9	72	28	11	2.1	9.6	11.9	25	77	36	no	no	no	no	no	no
127	ILAVARASI	F	39	A	7.9	1.6	70	24	9.5	2.1	8.4	11.4	15	78	34	no	no	no	no	no	no

127	JAYANTHAN	M	48	D	9.3	1.2	72	28	11	2.75	10.2	11.9	31	79	36	no	no	no	no	no	no
129	RAMYA	F	24	D	8.6	1.5	71	26	10	2.55	9.9	11.6	34	78	35	no	no	no	YES	no	no
130	ISAIPRIYA	F	11	D	7.2	1.3	70	23	9.5	3.1	8.7	11.8	31	79	35	YES	no	no	no	no	YES
131	POOVIKA	F	16	A	8.1	1.8	71	24	10	2.35	8.6	11.9	24	76	36	no	no	no	no	no	no
132	SANDEEP	M	25	A	9.1	1.2	71	27	10.5	2.1	9.9	12.6	36.5	79	38	no	no	no	no	no	no
133	VENNILLA	F	30	A	8.7	1	71	26	10	2.15	9.7	12.2	26	78	37	no	no	no	no	no	no

From

Dr. C. Krishnakumar MD Peds Post graduate student

Institute of Social Pediatrics,

Govt Stanley Medical College,

Chennai 600 001

To

The Dean,

Govt Stanley Medical College,

Chennai 600 001

Sub: reg. submission of thesis

Through proper channel

Respected Sir,

Herewith I'm submitting my thesis , "**A Comparative Study Of Efficacy Of Continuous Versus Intermittent Iron Therapy For The Treatment Of Iron Deficiency Anemia In Children Of Age Group 6 Months To 5 Years",** in partial fulfilment of the regulations for the award of MD degree.

Thanking you.

Place
Date

yours truly,

<u>சுய ஒப்புதல் படிவம்</u>

இரும்பு சத்து குறைபாடல் ஏற்படும் இராத்த சோகை நோய் சிகிச்சைக்கு, தினமும் மற்றும் இடைவிட்டு இரும்பு சத்து மருந்து கொடுக்கும் முறைகளை திறனை ஒப்பிடும் சோதனை.

ஆய்வாளர்: மரு.கிருஷ்ணகுமார் சின்னுசாமி

பட்ட மேற்படிப்பு மாணவர்

குழந்தை நலத்துறை

அரசு ஸ்டன்லி மருத்துவ கல்லூரி

சென்னை 600001

வழிகாட்டி: பேராசிரியர்: மரு. எஸ். இலக்ஷ்மி எம்டி, டிசிஎச்

குழந்தை நலத்துறை

அரசு ஸ்டன்லி மருத்துவ கல்லூரி

சென்னை 600001

பங்குபெரும் நோயாளின் விவரம்

பெயர்: வயது/பாலினம்:

மருத்துவமனை எண்:

இந்த மருத்துவ ஆய்வின் விவரங்கள் எனக்கு விளக்கப்பட்டது. எனது சந்தேகங்களை தீர்க்கவும் அதற்கான தகுந்த விளக்கங்களை பெறவும் வாய்ப்பளிக்கப்பட்டது.

நான் இந்த ஆய்வின் தனிச்சியாகதான் பங்கேற்கிறேன். எந்த காரணத்தினாலும் எந்த கட்டத்திலும் சட்ட சிக்கலின்றி இந்த ஆய்வின் இருந்து விலகிக்கொள்ளலாம் என்று அறிந்து கொண்டேன்.

நான் ஆய்வின் இருந்து விலகிக்கொண்டாலும் ஆய்வாளர் எனது மருத்துவ அறிக்கைகளை பார்ப்பதற்கோ அல்லது பயன்படுத்துவதற்கோ என் அனுமதி தேவைஇல்லை என்பதை அறிந்து கொண்டேன். என்னை பற்றிய தகவல்கள் ரகசியமாக பாதுகாக்கப்படும் என்பதை அறிவேன்.

இந்த ஆய்வின் மூலம் கிடைக்கும் தகவல்களும் பரிசோதனை முடிவுகளும் ஆய்வாளர் அவர் விருப்பத்திற்கேற்ப பயன் படுத்திக்கொள்ளவும் அதனை பிரசுரிக்கவும் முழு மனதுடன் சம்மதிக்கிறேன்.

இந்த ஆய்வின் பங்குகொள்ள சம்மதிக்கிறேன். எனக்கு கொடுக்கபட்ட அறிவுரைகளின்படி நடந்துகொள்ளவதுடன் ஆய்வாளருக்கு உண்மையுடன் இருப்பேன் என்று உறுதி அளிக்கிறேன்.

உடல்நலம் பாதிக்கபட்டால் அதனை தெரிவிப்பேன் என்று உறுதி அளிக்கிறேன். இந்த ஆய்வின் எனக்கு எந்த விதமான பரிசோதனைகளையும் சிகிச்சைகைக்கும் மேற்கொள்ள நான் முழு மனதுடன் சம்மதிக்கிறேன்.

இப்படிக்கு

நோயாளின் கையொப்பம் ஆய்வாளரின் கையொப்பம்

பெயர்

நோயாளின் தகவல் தாள்

இரும்பு சத்து குறைபாடல் ஏற்படும் இராத்த சோகை நோய் சிகிச்சைக்கு, தினமும் மற்றும் இடைவிட்டு இரும்பு சத்து மருந்து கொடுக்கும் முறைகளை திறனை ஒப்பிடும் சோதனை.

ஆராய்ச்சியின் நோக்கமும், ஆதாயங்களும்:

நம்மிடையே இரும்பு சத்து குறைபாடல் ஏற்படும் இரத்தசோகை நோய் அதிக அளவில் காணப்படுகிறது. இதை குணப்படுத்த கொடுக்கப்படும் இரும்பு சத்து மருந்து பக்க விளைவுகளை ஏற்படுத்துகிறது. இந்த மருந்திணை இடைவெளி விட்டு பயன்படுத்தும் போதும் தினமும் பயன்படுத்தும் பலனை அளிப்பதாக சில ஆராய்ச்சிகள் தெரிவிக்கின்றன. இது குழந்தைகளிலும் நிருபனம் ஆனால் அதிக பக்கவிழுவுகள் இன்றியும் எளிதாகவும் இந்த முறையை பயன்படுத்தி பலன் அடையாளம்.

ஆய்வு முறை:

இதில் உங்கள் குழந்தையின் குருதில், இரும்பு சத்து மருத்துவ சிகிச்சை கொடுப்பதற்கு முன்பும் பின்பும், இரத்தசோகை நோய்க்காண அளவீடுகளான ஹீமோகிலோப்பின், பெர்ரிடின் உட்பட அனைத்து தேவையான முக்கிய பரிசோதனைகள் செய்யப்படும்.

உண்டாகக்கூடிய இடர்கள்:

உங்கள் குழந்தையிடம் இருந்து மூன்று முறை 3 மிலி இரத்தம் எடுக்கப்படும். மேலும் இரத்தசோகை நோய்க்காண சிகிச்சைகாக இரும்பு சத்து மருந்து பரிந்துரைக்கப்பட்ட அளவில் பயன்படுத்தும் போது, வாந்தி, வயிர் எரிச்சல் போன்று அதற்குண்டான பக்கவிளைவுகள் ஏற்பட வாய்ப்புள்ளது.

ஆய்வில் உங்கள் உரிமைகள்:

உங்கள் மருத்துவ பதிவேடுகள் அந்தரங்கமாக வைத்துக்கொள்ளப்படும். இந்த ஆய்வின் முடுவுகள் அறிவியல் பத்திரிகைகளில் வெளியிடப்படலாம். இதில் உங்கள் பெயரோ அல்லது சொந்த தகவல்கள் வெளி வராது. ஆய்வில் பங்கேற்பது தனிசியானது மற்றும் காரணம் ஏதும் கூறாமலே நீங்கள் எப்போது வேண்டுமானாலும் விலகிக்கொள்ளலாம். எதுனும் பக்க விளைவுகள் ஏற்பட்டால் முழு சிகிச்சையும் மருத்துவ குழுவினரால் வழங்கப்படும்.

நாள் நோயாளின் கையொப்பம்

இடம் அல்லது இடது பெருவிரல் ரேகை